The Natural History of Columnar-Lined Oesophagus

Thesis for the Degree of MD

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Abstract

The incidence of oesophageal adenocarcinoma has increased faster than that of any other solid tumour over the last 50 years. The major aetiological factor associated with this tumour is prolonged gastro-oesophageal reflux resulting in metaplastic change in the squamous mucosa to a columnar mucosa (columnar-lined [Barrett's] oesophagus) with subsequent dysplasia and ultimately neoplastic change to adenocarcinoma. The natural history of this transformation is poorly documented and guidelines have only been developed recently to aid clinicians in their management of columnar-lined oesophagus.

This is a retrospective observational cohort study of 2751 patients from 7 United Kingdom centres collated through the UK National Barrett's Oesophagus Registry. It has followed the course of their progress preceding the diagnosis of columnar-lined oesophagus through the course of their clinical follow-up and endoscopic surveillance. The thesis is divided into 5 principal studies examining the natural history of columnar-lined oesophagus and its progression to adenocarcinoma and a sixth examining the validity of the database.

The project has examined demographic and epidemiological factors in columnar-lined oesophagus as well as overall rate of progression to adenocarcinoma. The importance of the length of the metaplastic segment and changes in this length and diagnostic histology with reference to malignant risk are examined and discussed. The progress of the metaplastic segment over time is examined with reference to the detection of dysplasia and adenocarcinoma at surveillance. The influence of antireflux treatment (medical and surgical) and symptomatic duration (and type) on the outcome of patients with columnar-lined oesophagus are described.

The project has provided a large cohort (the largest in the world with the exception of a pathology report-based database) for examination of the outcome of columnar-lined oesophagus which makes a significant contribution to knowledge on this subject to aid professional bodies in their guidelines and clinicians in their management of this condition.

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Chapter 1 – Introduction

Increase in Oesophageal Adenocarcinoma

There has been a global increase in the number of oesophageal cancers over the last 50 years, with the oesophagus being the 8th commonest site of primary carcinoma in 2000[1]. This increase has been demonstrated specifically in the United Kingdom[2-6] as well as in other countries[7-12]. The position of these cancers has changed from being distributed throughout the length of the oesophagus to cancers tending to develop in the lower part of this organ[3-5;8;10;13;14]. The histological type of these tumours has also changed, from historically a strong predominance of squamous cell carcinomata[15-18] to the present time, when adenocarcinomata make up the majority of oesophageal tumours in the Unites States and United Kingdom[4;5;19-23]. Consequently, oesophageal adenocarcinoma is the fastest increasing of all solid tumours[14].

Risk Factors for Oesophageal Adenocarcinoma

Oesophageal adenocarcinoma has been shown to be associated with older age[24-27], male gender[4;6;23-25;27-29], Caucasian ethnicity[7;14;23;25;27;30-32], higher social class[4], cigarette smoking[24;31;33-36] and obesity[31;33;34;37;38]. The strongest association is with prolonged gastro-oesophageal reflux disease[39].

In areas surrounding this neoplastic lesion: areas of abnormal oesophageal tissue have been found, where the normal native oesophageal squamous epithelium had been replaced by a columnar epithelium, also called Barrett's oesophagus after it was described by Norman Barrett in 1950 and 1957[40;41], similar in microscopic appearances to that found in the stomach or small intestine[42-44]. Often, these areas of metaplasia (the change in cell type) also harboured areas of pre-cancerous dysplasia[22;29;44-51], suggesting that the cancer had developed within the metaplastic area rather than directly from the oesophageal squamous mucosa. Animal models[52-58] and clinical (human) studies[59-68] have shown that patients who have developed columnar metaplasia within the oesophagus are those with the most severe gastro-oesophageal reflux disease suggesting that the sequence of events in the development of oesophageal adenocarcinoma is of prolonged gastro-oesophageal reflux leading to metaplastic change to columnar epithelium within the oesophagus, which with

further injurious reflux becomes dysplastic and finally neoplastic (i.e. cancerous). Once adenocarcinoma has developed, the majority of patients cannot be cured[8;69] as this aggressive tumour spreads locally and by metastasis to distant areas early in its course[70;71].

Natural History of Columnar-Lined Oesophagus and Surveillance

One autopsy study[72] and several clinical studies[59;73-83] have demonstrated that the population prevalence of columnar-lined oesophagus is 0.5%-37% (depending on the population studied and exact criteria for diagnosis); but fortunately, the majority of these patients do not develop adenocarcinoma[84-86] and one cancer will develop in 144 patient-years of follow-up (see appendix 1).

Studies have suggested that patients with the longest segments of columnar mucosa are those at highest risk of adenocarcinoma development[61;87-90], but the best indicator of risk of cancer is the finding of dysplasia[91-94] within the columnar segment. The annual risk of adenocarcinoma in patients with low-grade dysplasia is around 12%[47;95], whereas at the time of finding high-grade dysplasia, 43% of patients will already have developed an occult carcinoma[96] and the annual risk of adenocarcinoma development is 14-28%[90;97]. The only current reliable means of detecting dysplasia is endoscopy and biopsy[91;98] and the most widely accepted biopsy protocol is to take samples from each quadrant of the metaplastic segment at 1 or 2cm intervals[99]. Surveillance endoscopy can subsequently be undertaken to attempt to detect dysplasia and early cancer[91] as some studies have demonstrated that patients presenting with cancer in surveillance programmes have their tumours detected at an earlier stage[100-105] and have improved survival over patients diagnosed clinically (outside of surveillance programmes)[100-107]. Detection of high-grade dysplasia will also allow consideration to be given to radical therapy to attempt to cure adenocarcinoma prior to its development or spread[71;107-112], to localised treatment to ablate the metaplastic mucosa[113-115] or to performance of a localised resection[116] as a full oesophagectomy is associated with a significant risk of major complications[71;107;108].

However, surveillance is costly[117 118 119;120] and its benefits in detecting early stage lesions to allow curative treatment of adenocarcinoma have yet to be proven in a prospective study[121]. Subsequently, it has been proposed that a more appropriate strategy to surveillance would be to target surveillance to those patients at greatest risk of developing adenocarcinoma[122].

Prevention of Adenocarcinoma Development

The goal of treatment of columnar-lined oesophagus is to minimise reflux symptoms and maintain a healed mucosa[91]. The mainstay of treatment is medical suppression of gastro-oesophageal reflux with proton pump inhibitors[65;123;124] which reduce the volume and acidity of the refluxate[65;125], but do not prevent reflux of potentially damaging biliary or pancreatic secretions[65;126] and columnar metaplasia may still develop whilst patients are taking high-dose acid suppression treatment[127;128]. Additionally, some patients still have pathological acid exposure despite high-dose treatment[124;129;130]. Surgical treatment of gastro-oesophageal reflux re-establishes the physical barrier preventing exposure of the oesophagus to all possibly damaging reflux components[131-135] and two meta-analyses have demonstrated a trend for surgical therapy to be more efficacious than medical therapy in adenocarcinoma prevention[136;137]. However, concerns exist about the long-term failure rate of anti-reflux surgery, which may overcome the apparent early benefits[133;138].

UK National Barrett's Oesophagus Registry

The UK National Barrett's Oesophagus Registry was founded in 1996[139] to establish a register of patients throughout the United Kingdom with oesophageal columnar metaplasia to examine the natural history of this condition. This research project was undertaken on a subset of these patients and was designed to test 3 hypotheses:

1. That the natural history (length, histology and development of complications) of the columnarised segment changes with time.
2. That pharmacological, surgical and endoscopic therapy influences the natural history to differing extents.
3. That characteristics of Barrett's oesophagus patients at greatest risk of adenocarcinoma can be defined.

Data were collected from patients' hospital records over an 8 year period from 1996 to 2004 from 7 centres throughout the United Kingdom and entered onto a large database written specifically for this study by this author. Two thousand seven hundred and fifty one patients were involved in the study, of whom a full examination of the notes had been possible in 1651 cases. The database held information on diagnosis of columnar-lined

oesophagus, appearances over time when the oesophagus was examined endoscopically and of histological biopsies, presence of a bowel bacterium, *h pylori* (which has been associated with peptic ulcer disease and adenocarcinoma of the stomach), symptoms prior to diagnosis, treatment of gastro-oesophageal reflux, other medical and surgical conditions, medications taken, obesity, cigarette smoking and alcohol consumption. By manipulating the data stored, it was possible to examine associations between different factors and the clinical course of the columnarised oesophageal segment.

Chapter 2 – Review of Columnar-Lined Oesophagus

History of Columnar-Lined Oesophagus

In 1950, Norman Barrett (a surgeon at St Thomas' Hospital, London) published an article describing ulcerated gastric epithelium found in the alimentary tract in the thorax[40], which he initially thought to be due to a congenitally short oesophagus. The phenomenon of a gastric-type of lining associated with "oesophagitis" and ulceration had actually been described nearly 50 years previously by Tileston[140], and in the interim period by a number of other investigators[141-146]. Allison and Johnstone argued that the gastric epithelium was not actually lining an intrathoracic stomach, but the distal portion of the oesophagus due to the finding of areas of squamous epithelium in the same region, and the anatomical features of the lack of a peritoneal covering, presence of submucosal glands and a 2-layer (as opposed to 3 in the stomach) muscularis propria – all of which are features found in the oesophagus, but not the stomach[147;148]. In 1957, Barrett published his final report, when he concluded that the columnar-lined oesophagus was probably a failure of squamous re-epithelialisation of the oesophagus during development, but he did note the strong association with heartburn and possible development of adenocarcinoma in the metaplastic epithelium. He also noted the difficulty of differentiating between a true columnar-lined oesophagus and hiatus hernia[41].

Association of Columnar-Lined Oesophagus with Chronic Gastro-Oesophageal Reflux Disease

The association of columnar-lined oesophagus with symptoms of gastro-oesophageal reflux disease, hiatal hernia and oesophageal inflammation had been demonstrated by the 1970s[81;149-151]. This association has been shown in animal models, as well as by physiological measurements of oesophageal acid and bile exposure and correlation of these measurements with reflux symptoms.

Animal models of iatrogenic gastro-oesophageal reflux in the dog demonstrated that after mucosal injury, mucosal regeneration produced a columnar epithelium[52;53], which appeared to originate from deep oesophageal glands and was not just a proximal migration of the

cardiac columnar epithelium[54]. Further experiments demonstrated that reflux of duodenal contents also caused columnar metaplasia in both the dog[55] and the rat[56-58].

The clinical spectrum of gastro-oesophageal reflux disease varies from patients with no demonstrable abnormality of the oesophageal epithelium, to patients with inflammatory changes in the squamous epithelium and to patients with columnar metaplasia of the oesophagus (additionally, patients may be found to have changes of dysplasia or neoplasia in the oesophagus). In 1987, Winters *et al.* described a cohort of 97 patients with symptoms of gastro-oesophageal reflux (and an additional 21 patients who were known to have oesophageal columnar metaplasia) and found that the likelihood of associated oesophagitis was higher in those patients with columnar metaplasia than those patients with squamous epithelium[59]. Parilla *et al.*[60] showed that the lower oesophageal sphincter pressure (part of the antireflux mechanism) was lower and the magnitude of acid reflux was higher in patients with columnar-lined oesophagus over reflux oesophagitis and patients with normal oesophageal appearances. Avidan *et al.* demonstrated that the oesophageal acid exposure was higher in patients with Barrett's oesophagus compared to those with reflux oesophagitis and non-erosive reflux disease[61]. Champion *et al.*[62] showed that the magnitude of biliary reflux was higher in those patients with columnar metaplasia than in those with reflux oesophagitis, and this has also been demonstrated by aspiration of oesophageal contents by Stein *et al.*[63]. Kauer *et al.*[64] and Vaezi and Richter[65] showed that the combination of acid and biliary reflux was more frequently associated with findings of columnar oesophageal metaplasia than either alone. Csendes *et al.*[66] demonstrated that the oesophageal exposure to acid and bile was higher in those with long segment (>3cm) columnar-lined oesophagus than those with short segment columnar-lined oesophagus, which in-turn was greater than those with no columnarised segment of the oesophagus. Locke *et al.*[67] showed that the duration of reflux episodes were longer in patients with columnar-lined oesophagus than reflux oesophagitis. Lieberman *et al.*[68] demonstrated that patients with columnar-lined oesophagus had both a longer duration of symptoms and more frequent symptoms than those with oesophagitis or normal oesophageal appearances on endoscopy. However, many patients with columnar-lined oesophagus are relatively insensitive to oesophageal acid exposure[152] and asymptomatic oesophageal acid reflux is demonstrable in a proportion of these patients even when taking high-dose acid suppression medication[124;153;154]. There is also some evidence that a surgical antireflux procedure may protect against the development of columnar-lined oesophagus[127;155-157].

Association of Columnar-Lined Oesophagus with Oesophageal Adenocarcinoma

By the 1970s, the evidence demonstrated that in addition to the strong association with gastro-oesophageal reflux disease, the columnar-lined oesophagus had a more sinister association – with oesophageal adenocarcinoma[42-44]. The majority of this evidence arose from studies on resected oesophageal specimens, where the tissue surrounding the tumour demonstrated metaplastic columnar epithelium, frequently with areas of dysplasia[22;29;44-51], rather than from prospective follow-up of patients with columnar-lined oesophagus.
Animal models have demonstrated that in addition to inducing columnar metaplasia, surgical models of duodeno-gastro-oesophageal and duodeno-oesophageal reflux induce oesophageal cancer in rats[58;158-160] and proliferation of oesophageal cells following biliopancreatic reflux in rats[161]. Signs of proliferation of oesophageal cells have been induced following acid reflux in in-vitro human oesophageal biopsies[162].
Lagergren *et al.* showed in a population-based case-control study that the symptom of prolonged oesophageal reflux was the major risk factor for oesophageal adenocarcinoma[39], with an odds ratio of 7.8, rising to 43.5 in the patients with the longest and most severe symptoms of reflux. Chow *et al.*[163] confirmed this risk, but with a much lower odds ratio (2.5 for a reflux history of >5 years compared to no reflux symptoms).
Avidan *et al.* demonstrated that the magnitude of oesophageal reflux was higher in patients who developed high-grade dysplasia than those with columnar-lined oesophagus without dysplasia (which in turn was greater than in reflux oesophagitis and non-erosive reflux disease)[61].
Additionally, in two meta-analyses, elimination of gastro-oesophageal reflux by antireflux surgery in patients with columnar-lined oesophagus was associated with a trend for a lower risk of adenocarcinoma compared to those treated with medical antireflux therapy[136;137].
Conflicting evidence exists in the relative importance of duodeno-gastro-oesophageal reflux in the pathogenesis of oesophageal adenocarcinoma, with one series not demonstrating any difference in the proportion of patients with adenocarcinoma who had previously undergone gastric outlet surgery (allowing reflux of duodenal contents into the stomach and thence to the oesophagus) when compared to oesophageal squamous cell carcinoma[25]. A further series of follow-up of patients with columnar-lined oesophagus only reported adenocarcinoma development in patients who had previously undergone

gastric outlet surgery[89] and another demonstrated an increased risk of oesophageal adenocarcinoma development in patients who had undergone gastric outlet surgery at age under 45 years (especially in the period more than 20 years from the gastric outlet surgery)[164]. The development of oesophageal columnar metaplasia has not been shown to be increased following gastric outlet surgery[165;166], but the volume of biliary reflux has been shown to be higher in patients with oesophageal columnar metaplasia[62].
The relative risk of adenocarcinoma development in patients with columnar-lined oesophagus has been estimated at 30x[89] and 125x[92] that of the general Dutch population, 40x that of the US population [167], 30x the general UK population[168], 30x an age/gender-matched cohort in the UK[169] and 5x a control population in Northern Ireland[86].

Increased Incidence of Oesophageal Cancer

The incidence of oesophageal cancer has been increasing globally over the past 50 years. In 2000, the oesophagus was the 8th commonest site of primary carcinoma according to the International Agency for Research on Cancer (IARC)[1]. The areas with highest incidence of oesophageal cancer are Asia (North Iran-Central Asian Republics-North Central China), East and Southeast Africa, Eastern South America, and some areas of Western Europe (especially France and Switzerland). For the most part, in these areas, squamous cell carcinoma predominates, and these cancers are attributable to smoking, alcohol consumption, chewing tobacco, hot beverage drinking, nutritional deficiencies, opium or pipe-stem residues and dietary factors such as pickled vegetables, nitrosamine-rich foods and mycotoxins.

In England and Wales, overall cancer registry data[2] shows that the (age-standardised) incidence of oesophageal cancers has increased in males from 7.6/100,000 in 1971 to 12.8/100,000 in 1998 and in females from 4.2/100,000 to 5.7/100,000 over the same period. This occurred at the same time as a decrease in gastric cancers from 31.8/100,000 to 18.9/100,000 in males and 15.1/100,000 to 7.3/100,000 in females, (but regional registries have not demonstrated this fall in gastric cancers[3;4]). Hence, this change may in part be accounted for by a change in the trend of classification of tumours (from being of gastric to oesophageal origin), but the mortality associated with gastric cancer has fallen during this period, whereas that of oesophageal cancer has remained constant, suggesting that there is

an actual change in the anatomical disease location, rather than just a change in classification[170;171].

In the South-East of the UK, the Thames Cancer Registry[3] (age-standardised) incidence of oesophageal cancer showed an increase from 4.03/100,000 in 1960 to 9.00/100,000 in 1992 in males and 2.29/100,000 to 3.11/100,000 in females. Incidence of cancer of the gastric cardia has also increased over the same period.

The UK West Midlands cancer registry[4] has shown an increase in age-standardised oesophageal cancer incidence from 3.44/100,000 in 1962-66 to 4.37/100,000 in 1982-86. In the same period, gastric cancer rates have also increased from 9.19/100,000 to 12.48/100,000, with the most marked increase occurring in cardiac cancers (from 0.75/100,000 to 2.96/100,000). This makes the possibility of a change in trend of classification of anatomical site unlikely to be responsible for this increase in oesophageal cancer.

On a more local scale, a single centre in Berkshire (UK) serving a population of 360,000 has shown that the increase in the number of oesophageal malignancies diagnosed at oesophagogastroduodenoscopy parallels the increase in the use of upper gastrointestinal endoscopy, so that the rate of detection of oesophageal cancer per endoscopy undertaken remained constant, despite a four-fold increase in the number of endoscopies undertaken from 1976-80 to 1986-1990[5].

The Scottish Cancer Registry[6] has reported an age-adjusted increase in oesophageal cancer between 1960-62 and 1986-90 of 4.3/100,000 to 9.1/100,000 in males (an increase of 3.0% per annum) and 2.7/100,000 to 4.9/100,000 in females (an increase of 2.0% per annum).

The US National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER)[7] states that oesophageal cancer is the 11th highest malignant cause of person-years of life lost, with an average of 15.3 years lost per person dying of cancer. From 1992-2001, oesophageal carcinoma was the 7th fastest increasing site of malignancy, and 2nd fastest increasing malignant cause of death in the USA. From 1975-2000, the age-adjusted incidence had increased from 4.1 cases/100,000 per annum to 4.7/100,000. The increase in incidence has been mirrored by an increase in mortality. The US overall lifetime risk of being diagnosed with oesophageal cancer is 0.77%, and risk of death from oesophageal cancer is 0.73%[7]. Between 1988 and 1993, the US National Cancer Data Base also reports an increase in the prevalence of oesophageal malignancies[8].

In the Cote d'Or (Burgundy, France), the age-standardised incidence of oesophageal cancer has remained relatively static in men from 1976-78: 13.0/100,000 to 1991-93: 14.4/100,000. The number of oesophageal cancers in females was small, and reported to be approximately stable[9]. In 7 regions in France and neighbouring Switzerland in 1978-82, the annual (unadjusted) incidence of oesophageal cancer varied between regions from 9.0/100,000 to 29.9/100,000 in males and 0.6/100,000 to 2.1/100,000 in females[10].

The Danish cancer registry demonstrates that the overall incidence of oesophageal cancer fell from 1943-1960, after which the overall rate remained fairly constant to 1987[11].

In Norway, cancer registry data has shown an age-standardised increase in annual incidence of oesophageal cancer from 2.6/100,000 in 1958-62 to 3.0/100,000 in 1991-92 in males, and 0.6/100,000 to 0.8/100,000 in females. The increase in males was still apparent when oesophageal and gastric cardia cancers were combined, but there was no overall change in females when these two locations were combined[12].

In addition to the increasing overall incidence of oesophageal cancer, the histological cancer types and location have also changed with time. The World Health Organisation (WHO) International Classification of Diseases (ICD) 9th Edition[170] classified adenocarcinomata of the oesophagus with those of the gastric cardia, and it was not until the first WHO ICD-Oncology classification in 1976[171] that adenocarcinoma originating in the oesophagus was widely acknowledged as a separate entity from gastric cardiac adenocarcinoma and began to be coded separately in registries.

Change in Anatomical Location of Oesophageal Cancers

At the same time as the change in oesophageal cancer incidence, there has also been a change in the anatomical location of cancers within the oesophagus – which have traditionally been classified as those in the upper third (above the carina), middle third (from this point to 32cm from the incisors or the level of the 9th thoracic vertebra) and lower third (from 32cm to the oesophagogastric junction)[172]. In the above section, I have demonstrated that the increase in overall oesophageal cancer incidence cannot be explained

by cancers previously being classified as originating in the gastric cardia more recently being classified as being in the distal part of the oesophagus. This increase in cancers is accounted for by those developing in the distal third of the oesophagus.

The UK West Midlands cancer registry has shown a five-fold increase in cancers of the lower third in the 20 year period 1962-66 to 1982-86, whilst the incidence of cancers of the upper two thirds has remained constant in the same period[4].
The UK North-West cancer registry examined the sub-site of 1067 oesophageal cancers diagnosed in 1993, and reviewed hospital records to increase accuracy. This study demonstrated that the majority of cancers occurred in the distal third of the oesophagus or traversed the gastro-oesophageal junction. When oesophageal adenocarcinomata were examined specifically, 85.8% of those of oesophageal origin were in the lower third[13].
The Thames cancer registry's age-standardised oesophageal cancer incidence has shown a trend to increase in the upper two thirds from 1960 to 1996 (0.59/100,000 to 1.09/100,000 in males and 0.30/100,000 to 0.70/100,000 in females) and a statistically significant increase in the lower third (0.93/100,000 to 3.43/100,000 in males and 0.42/100,000 to 0.91/100,000 in females)[3].
The Berkshire single centre has demonstrated that the majority of adenocarcinoma originate in the lower third of the oesophagus and that there has been a trend for the proportion of adenocarcinomata located in the distal third to increase during the 15 year period of the study[5].

In the US, the proportion of oesophageal cancers arising in the distal third has increased from 40.8% of all oesophageal cancers in 1988 to 48.1% in 1993[8]; and in 1991, 81%[14] of oesophageal adenocarcinomata arose in the distal third.

In the Cote d'Or, France, there were no significant variations in the incidence of cancers in the separate thirds of the oesophagus[9], however 3 of the 7 regions in France and Switzerland reported by Tuyns showed an increase in the proportion of oesophageal cancers arising in the distal third[10].

The Norwegian cancer registry reported no significant change in the incidence of adenocarcinomata of the upper two thirds, but an increase of 16.9% per annum in adenocarcinomata of the distal third in males, and a similar trend in females[12].

Increase in Oesophageal Adenocarcinomata

The rise in oesophageal cancers (of all histological types) in the US is due to the increase in adenocarcinomata, which are most frequently located in the distal portion of the oesophagus as discussed above. From 1926-1976, 4 surgical series demonstrated that the proportions of all oesophageal cancers which were histologically adenocarcinomata ranged from 0.8% to 3.7%[15-18]. In 6 series from 1979-1998, the proportion of oesophageal adenocarcinomata had risen to become the majority of oesophageal cancers in the US and UK[5,19-23].

The UK West Midlands cancer registry has shown an increase in age-standardised oesophageal adenocarcinoma incidence from 0.14/100,000 in 1962-66 to 0.76/100,000 in 1982-86. In the same period, oesophageal squamous cell carcinoma has also increased from 1.90/100,000 to 2.48/100,000, and anaplastic/unspecified type increased from 0.18/100,000 to 0.37/100,000. These increases may be partially offset by a decrease in the number of tumours coded without histology (1.22/100,000 decreased to 0.76/100,000)[4].
The UK North-West cancer registry showed that in 1993 38.1% of oesophageal cancers were adenocarcinomata, which was a smaller proportion than squamous cell carcinomata (44.1%), (with the remaining 17.8% classified as "unknown", "other" or "unspecified")[13].
The single centre study in Berkshire, UK has shown an overall increase in endoscopically-diagnosed oesophageal cancer incidence, but the proportion of adenocarcinoma has remained constant at 50% throughout the study period 1976-90[5].
The Scottish cancer registry[6] has reported an increase in the age-adjusted annual incidence of adenocarcinomata between 1976 and 1989 of 2.2/100,000 to 3.5/100,000 in males and 0.8/100,000 to 1.1/100,000 in females. These have been accompanied by similar rises in squamous cell carcinomata in both genders, and also an increase in the proportion of histologically-verified tumours – but not sufficient to compensate for the overall increase in oesophageal cancer.

The US SEER database was analysed initially in 4 year bands by Blot *et al.* in 1991[14] and demonstrated an increase in the incidence of oesophageal adenocarcinoma of 9.4% per annum in white males, 9.8% per annum in black males and 4.5% per annum in white females (the number of oesophageal adenocarcinomata in black females was too small to allow meaningful analysis). They state that this was the fastest increasing malignant disease in their database during this period. These trends continued through to a further analysis of the data to 1994[23].

El-Serag *et al.*[27] looked at the histological subtypes and anatomical locations of the SEER database cancers, and found an increase in the age-standardised adenocarcinoma rate in 5 year bands from 1977-81 (1.8/100,000) to 1992-96 (3.1/100,000). In part, some of this increase could be attributed to changes in the trend to classify oesophageal adenocarcinomata as arising from the gastric cardia (but the incidence of gastric adenocarcinoma has remained static during the 20 year study period, whilst the rate of oesophageal adenocarcinoma has continued to rise progressively throughout the study period). The ageing population should not be a significant source of bias due to the adjustment of the figures to a standardised population; and furthermore, there has also been an increase in the rate of oesophageal adenocarcinoma in younger patients (organised into 5 year age bands). The US National Cancer Data Base reports an increase in the proportion of adenocarcinoma of the oesophagus compared to all oesophageal cancers of known histological type from 33.2% in 1988 to 43.1% in 1993[8]. In 3 major hospitals in Atlanta, Georgia, USA[22], adenocarcinomata outnumber squamous cell carcinomata by 2:1, in white patients, but only represent 5% of oesophageal cancers in black patients.

In the Cote d'Or (Burgundy, France), the proportion of adenocarcinomata as a fraction of all oesophageal malignancies is much lower than in the UK or USA (at 11% overall during the study period), but the age-standardised incidence of adenocarcinomata in males rose from 0.7/100,000 in 1976-78 to 3.9/100,000 in 1991-93[9]. In the South of France and 2 neighbouring Swiss cancer registries, the proportion of adenocarcinomata amongst all oesophageal cancers varies between 3.6% and 29.9%[10].

The Swedish population-based registry reports an annual age-adjusted incidence of 1.1/100,000 in males[173].

From 1978 onwards, the Danish registry commenced utilising ICD-O classification of tumours[171]. This period demonstrated an increase in the annual incidence of oesophageal adenocarcinoma from 0.78/100,000 to 1.29/100,000. However, the authors note that caution must be employed as a large number of cases were reported to the cancer registry without information on tumour histological type or exact anatomical location[11].

In Norway, oesophageal adenocarcinoma age-standardised incidence has increased from 0.3/100,000 in 1983-84 to 0.9/100,000 in 1991-92 in males and 0.0/100,000 to 0.1/100,000 in females. Although the actual incidences are low in both genders, the overall annual rate of increase is 16.6% in males and 14.4% in females[12].

There was a trend for an increase in oesophageal adenocarcinoma in non-Maori men and women from 1978-92 in New Zealand (similar to that in the US)[174] and in all states of Australia from 1982-93[175].

In the far East, this trend has not been apparent. In Taiwan, the incidence of oesophageal adenocarcinoma has not changed significantly or increased as a proportion of all oesophageal malignancies over the last 15 years[176]. In China, adenocarcinoma still only represents 3% of total oesophageal malignancies[177] and 6% in Southern Thailand[178].

Unfortunately, in addition to the incidence of adenocarcinoma of the oesophagus rising, this malignant disease frequently presents late and is incurable at presentation[2;8;69].

Definition of Columnar-Lined Oesophagus

The definition of columnar-lined oesophagus or "Barrett's oesophagus" differs between the UK and USA, the latter requiring a specific mucosal subtype. There are 3 subtypes of columnar metaplasia of the oesophagus described by Paull *et al.* in 1976[179]:

1. fundic: columnar epithelium with parietal cells and chief cells at the deep glandular layer
2. cardiac: mucous secreting columnar cells
3. specialised intestinal metaplasia: goblet cells (seen to stain positively with Alcian blue), which may be of complete type (with the presence of Paneth cells), or much

more commonly incomplete type (with fusion of intestinal-type goblet cells and gastric-type mucin-secreting cells)[180].

The American College of Gastroenterology defines "Barrett's oesophagus" as "a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia of the tubular esophagus and excludes intestinal metaplasia of the cardia"[91;181]. The rationale for the requirement of this specific epithelial subtype for the diagnosis of "Barrett's oesophagus" was that specialized intestinal metaplasia was the epithelium associated with dysplasia surrounding adenocarcinoma[45] as well as adenocarcinoma itself[29;44-46;48-50;87;182-187]. In the UK, the national guidelines on the diagnosis and management of columnar-lined oesophagus have only recently been published by the British Society of Gastroenterology[121]. These recommend that "the clinician should discuss with the patient the possible benefits of surveillance" of any macroscopic columnarised segment, irrespective of the subtype of columnar mucosa demonstrated at biopsy. These guidelines classify biopsies into 4 categories[121;188]:

1. diagnostic for columnar-lined oesophagus (showing native oesophageal structures with juxtaposition to glandular mucosa)
2. corroborative of an endoscopic diagnosis of columnar-lined oesophagus (showing columnar mucosa with intestinal metaplasia, but no native oesophageal structures and hence could represent a biopsy of intestinal metaplasia of the cardia or the stomach/a hiatus hernia)
3. biopsies in keeping with, but not specific for columnar lined oesophagus (showing columnar mucosa without intestinal metaplasia, which could be taken from the gastro-oesophageal junction or the stomach/a hiatus hernia)
4. biopsies without evidence of columnar-lined oesophagus (squamous epithelium, without evidence of columnar epithelium).

In addition to the definition of the type of metaplastic epithelium, dysplastic changes are also categorised. Following the pathology meeting prior to the World Congress of Gastroenterology in Vienna in 1998, unification of classification of dysplasia and neoplasia throughout the gastrointestinal tract into 5 categories was proposed[189]:

1. no dysplasia
2. indefinite changes for dysplasia

3. low-grade dysplasia
4. high-grade dysplasia
5. carcinoma

Previously, short segments of columnar-lined oesophagus were frequently excluded from surveillance. This was due in part to difficulty in determining the presence and extent of the segment[190] and also the possibility of "false positive" diagnosis of columnar-lined oesophagus[190]. Difficulty in accurately visualizing the oesophagogastric junction where the tubular oesophagus flares into the saclike stomach[191], variation in the distance measured from the incisor teeth to this point (due to respiration, peristaltic activity and prolapse of the gastric folds into the oesophagus)[192] and the degree of distension of the oesophagus and stomach (due to insufflated air from the examining endoscope) will also cause variation in measurement of this level[192]. Barrett himself noted that the presence of a hiatus hernia may mimic a columnar-lined segment of oesophagus[41] and this anatomical lesion can confuse accurate localization of the oesophagogastric junction when it is recognized[190]. Furthermore, in 1961, Hayward had stated that the normal oesophagus could be lined by gastric-type epithelium for 1-2cm at its lower end[193] and despite the fact that he did not cite any studies or personal investigations to support this view, this paper was frequently cited as evidence that a short columnarised segment was a normal variant, and not a true "Barrett's oesophagus".

The proximal extent of the columnar-lined segment is also subject to variation in measurement due to the same movement artefacts as the oesophagogastric junction, but also variations in determination of the position of the junction between the metaplastic columnar epithelium and native oesophageal squamous epithelium. This level may be concealed or blurred by the presence of inflammation[194;195], the presence of islands of squamous mucosa within the columnar-lined segment or vice versa, or non-circumferential tongues or streaks of columnarised mucosa extending proximally[196]. Significant inter- and intra-observer variation in measurement of the segment length has been demonstrated both in-vivo[197-199] and in-vitro[200]. "Short-segment" columnar-lined oesophagus has been variously defined as $\leq$2cm[201] to $\leq$5cm[202], with the majority of authors using <3cm [91;192] or $\leq$3cm[122] as their defining cut-off. Although the shorter length of columnar lining might initially suggest that the oesophageal insult from reflux is of smaller magnitude, short segments of columnar-lined oesophagus are more frequently associated with active

inflammation[203]; and a region of acidic reflux overlying a meal in the stomach has been demonstrated in-vivo and in-vitro immediately above the gastro-oesophageal junction with buffered (less acidic) reflux proximal and distal to this region[204].

Following the 2004 United European Gastroenterology Week, publication is awaited on the Prague "C & M endoscopic grading of Barrett's Esophagus". This will define 3 landmarks for the description of a columnar-lined oesophageal segment: the oesophagogastric junction, extent of circumferential(C) columnar lining above the oesophagogastric junction (excluding any squamous islands) and maximal extent of the columnar lining above the oesophagogastric junction (M).

Prevalence of Columnar-Lined Oesophagus

The prevalence of histologically confirmed columnar-lined oesophagus at the single Berkshire centre has increased over and above the increase in frequency of performance of upper gastrointestinal endoscopy, being diagnosed at 12/6,500 (0.2%) endoscopies in 1977-81 and 267/16,500 (1.6%) endoscopies in 1992-96[73]. When the incidence of new cases of columnar-lined oesophagus was examined in this region and an adjacent region on the Thames valley, the rates were 54.7/100,000 and 25.4/100,000 (respectively) per annum[74]. In the Tayside region of Scotland, the incidence of endoscopically diagnosed >3cm columnar-lined oesophagus has increased from 1/100,000 per annum in 1980-81 to 48/100,000 in 1992-93[75].

In Dublin, Republic of Ireland, 74 (37%) of 200 patients undergoing upper gastrointestinal endoscopy had a macroscopic segment of columnar-lined oesophagus, 63 of whom had a segment height <3cm and 11 ≥3cm. Intestinal metaplasia was demonstrated in 15 (24%) of those with <3cm and 8 (73%) of those with ≥3cm segment columnar-lined oesophagus. No patients had features of dysplasia [76].

In the US, it is estimated that between 19.8%[205] and 29.1%[206] of Americans suffer frequent heartburn. Twelve percent of patients with symptoms of longstanding reflux had at least a 2cm streak of columnar mucosa with intestinal metaplasia on biopsy[59], and 12% of males had at least 4cm of metaplastic columnar mucosa (7% with intestinal metaplasia)[77]. In 110 asymptomatic patients undergoing screening for colorectal cancer, the prevalence of

columnar intestinal metaplasia of the oesophagus was 25% (27 patients, 8 with ≥3cm segments)[78]. A landmark study conducted at the Mayo Clinic, Olmsted County, Minnesota[72] reported that the clinical prevalence of columnar-lined oesophagus extending at least 3cm with intestinal metaplasia was 22.6 cases per 100,000 population. Although the frequency of this diagnosis was increasing, this was occurring in parallel to the increased frequency of the use of upper gastrointestinal endoscopy in the institution (unlike in the Berkshire study above). The prevalence in an autopsy series of 226 patients at the same institution (examining the dissected cadaver with an endoscope) demonstrated a new diagnosis of ≥3cm columnar-lined oesophagus with intestinal metaplasia in 5 of these cases (from the clinical prevalence, the expected number would have been 0.19) which would suggest an occult prevalence of 1 in 76 patients in this area, a 21-fold increase on the known prevalence of clinical cases. In 1998, the estimated clinical prevalence at the same institution was 80/100,000 – one fifth of the autopsy-found prevalence[207]. The proportion of patients undergoing upper gastrointestinal endoscopy who were diagnosed with columnar-lined oesophagus of greater than 3cm, or intestinal metaplasia on histological examination was 113/2641 (4.3%). Another US endoscopy-based study reported a prevalence of <3cm of columnar-lined segment of 6.0% and ≥3cm of 1.6%[79].

A large Italian multi-centre cohort demonstrated a population prevalence of 1.01% of males and 0.74% of females[80] undergoing gastrointestinal endoscopy.
In Switzerland, a historical series published in 1975 by Naef *et al.*[81] demonstrated columnar-lined oesophagus in 130 of 1225 (10.6%) patients presenting for upper gastrointestinal endoscopy with reflux symptoms.

Forty six of 158 (36%) of unselected patients who underwent upper gastrointestinal endoscopy at a single centre in Australia demonstrated specialised intestinal metaplasia on biopsy of the gastro-oesophageal junction, but only 4/183 (2.2%) had a segment length ≥3cm[83].
An early cohort of patients referred to a regional thoracic surgical centre in Dunedin, New Zealand for management of hiatus hernia demonstrated columnar-lined oesophagus in 45/1,000 (0.45%) of patients[150]. Ten years later, the same institution reported that 10% of patients with gastro-oesophageal reflux at endoscopy had columnar metaplasia of the oesophageal mucosa[82].

A gastrointestinal symptom questionnaire sent to residents of Singapore showed a much lower prevalence of reflux symptoms than in Western countries, which were lower in ethnic Chinese (0.8%) and Malays (3.0%) than Indians (7.5%)[208]. A study from neighbouring Malaysia demonstrated columnar-lined oesophagus in 6.2%, also higher in ethnic Indians than Malays or Chinese[209].

In Japan, 5 (5%) of 103 oesophagectomy specimens for squamous cell carcinoma of the thoracic oesophagus demonstrated short segment columnar-lined oesophageal segments, 4 of which also had intestinal metaplasia[210].

In South Korea, the prevalence of columnar-lined oesophagus was only 5 (0.3%) of 1553 unselected patients referred for oesophagogastroduodenoscopy[211].

An Indian cohort showed a very high prevalence of columnar-lined oesophagus: 63 (42%) of 150 patients with symptoms of dyspepsia had columnar-lined oesophagus, but only 4 (2.6%) had intestinal metaplasia[212].

A retrospective analysis of patients with columnar-lined oesophagus in Johannesburg, South Africa between 1970-93 demonstrated that only 11 (5%) of 216 patients were black, despite the ethnic ratio of blacks: whites of 5:1[213].

A retrospective study of 2572 patients at a single centre in Saudi Arabia who had undergone upper gastrointestinal endoscopy demonstrated 8 (0.3%) patients with biopsy proven columnar-lined oesophagus[214].

Epidemiological Associations of Columnar-Lined Oesophagus

Age

A large study from Olmsted County, Minnesota, USA demonstrates that the prevalence of columnar lined oesophagus increases with age[215]. Half of the maximum prevalence was reached at age 40 years (although this is in the selected population undergoing upper gastrointestinal endoscopy). The authors suggest that this is the average age of acquisition of the metaplastic epithelium, and so with their average age of diagnosis at 63 years, they also make the supposition that the metaplastic segment has "probably been present for more than 20 years already" by the time of diagnosis. The large Italian multicentre cohort demonstrated that the highest decade of patient age at diagnosis is 70-79[80]. A large UK general practitioner cohort of patients with "Barrett's oesophagus" had mean age 61 years in males and 67 in females[169], and other studies have demonstrated that the average age at diagnosis typically lies in the sixth and seventh decades of life[36;47;79;84;85;85;87;88;94;138;168;168;216-224]. Patients with columnar-lined oesophagus are generally older than those with reflux oesophagitis[224].

Gender

Cameron *et al.* found that the prevalence of columnar-lined oesophagus in patients undergoing upper gastrointestinal endoscopy was twice as high in men compared to women[215] and even higher rates have been reported by military and veterans' hospitals[36;78;79;224;225]. A large Italian study showed a male: female ratio of 1.3:1[80]. The UK general practitioner-based cohort had a male: female ratio of 1.6:1[169], and large pathology-based study in Northern Ireland 1.3[216]. A large European study of 702 patients had a ratio of 2.1:1[217]. Compared to patients with reflux oesophagitis, patients with columnar-lined oesophagus are more likely to be male[224].

Ethnicity

Columnar-lined oesophagus is more commonly found in Caucasians than other races[79], with much lower rates in Afro-Caribbeans, Asians and other ethnicities[208;209;213]. Many of

the studies on columnar-lined oesophagus in the US have originated from military and veterans' hospitals treating mainly white veterans[36;78;79;225;226] and have demonstrated a high incidence of columnar-lined oesophagus in these patient groups. The bias from referral patterns of these patient groups should be balanced against interpretation of the high rate of metaplastic segment incidence in these patients (as with the data on gender).

Social Class

Unlike adenocarcinoma of the oesophagus, there is little data in the literature on socioeconomic status and columnar-lined oesophagus. One study suggests that patients with columnar-lined oesophagus had a higher level of education when compared to a control cohort[227].

Alcohol

Studies have not demonstrated an association between alcohol consumption and development of columnar lined oesophagus[217;227;228], and alcohol consumption is also similar to that in patients with reflux oesophagitis[224;229].

Smoking

Studies have not demonstrated an association between smoking habits and development of columnar lined oesophagus[217;227;228] and smoking habits are also similar to those of patients with reflux oesophagitis[224;229].

Obesity

Studies have not demonstrated any difference between patients with columnar-lined oesophagus and controls[78;169;217].

Epidemiological Associations of Oesophageal Adenocarcinoma

Age

The peak decade of diagnosis is septuagenarians in both males and females[24-26], and the incidence increases with age (and year of birth)[27].

Gender

In both the UK and US, the incidence of oesophageal adenocarcinoma is higher in males than females[4;6;23-25;27-29] by a ratio of 3-10:1.

Ethnicity

In the US, oesophageal adenocarcinoma has been shown to be more common in white than black Americans[7;14;23;25;27;30-32].

Social Class

In the UK, oesophageal adenocarcinoma is rising more rapidly in social classes I and II than III-V[4], whereas in the US, higher earning and graduate school education were associated with a lower risk[24;31;34].

Alcohol

Some data have demonstrated a relationship between alcohol consumption and oesophageal adenocarcinoma, comparing both alcohol drinkers to non-drinkers (odds ratio 1.6-2.3)[33;34], and a higher alcohol consumption (≥21 units/week) has been shown to be more strongly associated with adenocarcinoma than moderate consumption (odds ratio 2.8)[31]. One large study has shown the converse: that alcohol drinking overall is associated with a lower risk of adenocarcinoma[24].

Smoking

Patients with oesophageal adenocarcinoma were more likely to smoke than matched control populations (odds ratio 2.1-3.4)[24;31;33-35], with a stronger association for heavier smokers[35], and a weaker (but still significant) association for ex-smokers[35;36].

Obesity

There is some epidemiological evidence of an association between oesophageal adenocarcinoma and obesity[34;37], which is strongest for patients in the highest quartile[33;37;38] or decile[31] of body mass index when compared to a control population.

Comparison of Oesophageal Adenocarcinoma With Squamous Cell Carcinoma

Compared to patients with squamous cell carcinoma of the oesophagus, patients with adenocarcinoma tend to be younger[26;34], higher earners/in a higher social class/have more education[24;31;34], lighter smokers[24;26;31;34], drink less alcohol[24;26;31;34] and are more likely to be white[14;25] and obese[31;34;37].

Surveillance of Columnar-Lined Oesophagus

The American College of Gastroenterology states: "The goal of surveillance in Barrett's esophagus is the detection of dysplasia and early cancer", and advocates that "Patients with Barrett's esophagus are candidates for surveillance if there is a potential to prolong life expectancy with a therapeutic intervention for early cancer"[91]. However, studies have not demonstrated an increase in mortality or adenocarcinoma incidence over either patients with reflux oesophagitis or achalasia[230] or in age/gender-matched cohorts[86;89] or population-based cohorts[86;221]. Furthermore, less than 5% of patients with columnar metaplasia of the oesophagus die from oesophageal adenocarcinoma[84-86].

Adenocarcinomata detected within surveillance programmes are at an earlier stage than those presenting clinically[100-105] and have improved survival over cancers diagnosed outside of surveillance programmes[100-107]. In a series of patients undergoing yearly surveillance

with 4-quadrant biopsies every 2cm (or 3-6 monthly surveillance if dysplasia was present), all 3 patients who developed high-grade dysplasia or adenocarcinoma were detected at an early stage (most advanced stage: T1) and underwent oesophagectomy, with no known residual disease[100]. In another study, 17 patients undergoing surveillance (initially with biannual endoscopy and no specific biopsy protocol, then later annual endoscopy with 4-quadrant biopsies every 2cm) developed adenocarcinoma. Eleven of these patients had high-grade dysplasia or T1 N0 superficial adenocarcinoma, 3 had T2-T3N0, and one had nodal involvement. Four of these patients died: 2 postoperatively and 2 from recurrent adenocarcinoma (with the remaining 13 alive and adenocarcinoma-free at a median follow-up of 31 months)[103]. In other studies, the surveillance protocol is not clear, but the survival at 2 years in surveillance-detected adenocarcinomata has been reported as 73.3%[104] and 85.9%[102] and at 5 years as 60%[107]; and median survival 107 months (with 75% of surveillance-detected adenocarcinomata being staged T0-T1N0)[105]. Furthermore, patients who have previously undergone upper gastrointestinal endoscopy have an inverse association with death from oesophageal adenocarcinoma[30]. Despite rigorous surveillance protocols, cancers are still frequently diagnosed at unscheduled extra surveillance endoscopies[230].

Dysplasia is the best current indicator of risk of cancer[91], and is the basis upon which surveillance frequency is determined.

Adjuncts to surveillance include mucosal staining techniques, magnification endoscopy and balloon [231] and brush[231-234] cytology. Mucosal staining with Lugol's iodine[235], toluidine blue[236], indigo carmine[237] and methylene blue[238] help targeting of biopsies to areas of intestinal metaplasia. Magnification endoscopy demonstrates surface patterns more associated with underlying intestinal metaplasia and dysplasia[239-241]. Mucosal fluorescence has shown some early promising results in targeting areas of dysplasia for biopsy[242;243]. However, these techniques are still for the most part unvalidated[98], and are not widely available in clinical practice and subsequently diagnostic and surveillance practice is currently based on standard endoscopy and biopsy.

Cost of cancer detection compared to mammographic surveillance for breast cancer was comparable; and cost per quality-adjusted life year gained was much lower than for breast cancer[117], but the estimated adenocarcinoma incidence was very high (1/73 patient-years) in this model. A second model used a lower adenocarcinoma incidence (1/227 patient-years), and still demonstrated that the cost per quality-adjusted life year gained by endoscopic

surveillance was comparable to heart transplantation and targeted tuberculosis screening[118]. The overall cost of surveillance and medical treatment is estimated to be comparable to insulin-dependent diabetes[119]. A further US study of surveillance cost reported that with the inclusion of costs of one-off screening, surveillance (if columnar-lined oesophagus was detected), treatment of gastro-oesophageal reflux disease and adenocarcinoma treatment (both radical and palliative) was comparable between screening (US$1.2 billion per 100,000 population over age 50) and no screening (US$1.1 billion per 100,000 population)[120]. These figures must be interpreted with caution as the model is highly sensitive to variations in the incidence of columnar-lined oesophagus and adenocarcinoma, and additionally does not take into account time taken off from work to attend the hospital or psychological cost of screening and surveillance.

The American College of Gastroenterology[91] recommends surveillance with oesophagogastroduodenoscopy and systematic biopsy (for example 4-quadrant every 2cm of metaplastic epithelium[99]) repeated; and then a surveillance interval based upon the most dysplastic features demonstrated:

> No dysplasia: Repeat in 3 years
>
> Low-grade dysplasia: Repeat in 1 year
>
> High-grade dysplasia: Repeat and if only single focus of high-grade dysplasia then repeat in 3 months; if multiple areas or mucosal irregularity then proceed to intervention (photodynamic therapy, endoscopic mucosal resection or oesophagectomy).

Surveillance is costly (as discussed above) and time-consuming. Actual surveillance practice differs from the recommendations of the US guidelines. In the UK, a survey of gastroenterologists at the British Society of Gastroenterology in 1997 reported that 70% performed surveillance for columnar-lined oesophagus at varying intervals, with only 9% taking 4-quadrant biopsies every 2cm[244]. A similar survey in 2001 demonstrated that 76% of gastroenterologists believed that surveillance of columnar-lined oesophagus was worthwhile. However, many based their surveillance interval on segment length, and 12% described their follow-up interval as "variable". Biopsy protocol also varied enormously, with 59% biopsying randomly or suspicious areas only[245]. Reports from individual centres demonstrate that they had no formal surveillance programme (particularly with reference to inclusion criteria, endoscopic interval and biopsy protocol), or have only implemented one relatively recently both in the UK[100;103;183] and abroad[87]. In the US, surveillance is more

widely practiced, with 96% of gastroenterologists offering surveillance at varying intervals, but with the majority (77%) taking 4-quadrant biopsies every 1 or 2cm throughout the segment[246].

The US guidelines[91] recommend surveillance of all visible columnar metaplasia which demonstrates intestinal metaplasia on biopsy as this is the metaplastic tissue type most frequently found surrounding adenocarcinoma[29;44-46;48-50;87;182-187]. Intestinal metaplasia does not have any distinguishing features from cardiac or fundic metaplasia of the oesophagus when viewed with a standard endoscope and so its presence is sought on histological examination of biopsy specimens. Whilst the importance of intestinal metaplasia in the sequence of events leading to adenocarcinoma is well-accepted, the events leading to intestinal metaplasia are less well understood. Studies have demonstrated that the prevalence of detected intestinal metaplasia increases with patient age[247;248], cumulatively with number of surveillance endoscopies[249], increased length of gastro-oesophageal reflux symptoms[250], increased oesophageal exposure to bile[250] and macroscopic length of columnarised segment[249;251;252]. The finding of goblet cells is subject to significant sampling error[197;252-255] and increases with the experience of the endoscopist[254] and number of biopsies taken from the metaplastic segment[256]. Additionally, patients who were first diagnosed with columnar-lined oesophagus without intestinal metaplasia have subsequently demonstrated intestinal metaplasia on further surveillance biopsies and later progressed to adenocarcinoma[87]. Csendes *et al.*[186] have identified a subset of patients who progressed from fundic metaplasia to cardiac metaplasia to intestinal metaplasia, whereas Chandrasoma *et al.*[252] suggest that the pathway of metaplasia is from squamous to cardiac to either intestinal-type or oxyntic-type (fundic) epithelium. Furthermore, histochemical markers of intestinal differentiation have been demonstrated in biopsy specimens without the presence of goblet cells[257]. Pathological opinion in the UK recommends surveillance of all columnar metaplasia of the oesophagus, irrespective of the mucosal subtype[121;256] and in 1997 only 12% of UK clinicians undertaking surveillance based this on the presence or absence of intestinal metaplasia[244].

Rate of Progression of Columnar-Lined Oesophagus to Adenocarcinoma

Fortunately, the rate of progression of columnar-lined oesophagus to adenocarcinoma is low, and has been variously reported as no adenocarcinomata development in 410 patient-years of follow-up[138] to 43 adenocarcinoma in 1,200 patient years of follow-up (or 3.6% per annum)[47]. Appendix 1 shows the results from 40 papers reporting adenocarcinoma incidence from an extensive literature search including reviewing the bibliographies of the papers selected. The overall adenocarcinoma incidence in patients with columnar-lined oesophagus was 0.69% per annum (95% confidence interval calculated using the exact Poisson distribution 0.60-0.79%).

Higher rates of progression have been reported in patients with longer segments of columnar metaplasia, those who had dysplasia on histological examination and those who had mucosal ulcers, nodules or irregularity visible macroscopically with the endoscope.

Segment Length and Adenocarcinoma Risk

A case-control study[61] comparing patients with high-grade dysplasia or oesophageal adenocarcinoma to a cohort of patients with columnar lined oesophagus found that the high-grade dysplasia/adenocarcinoma metaplastic segment length was longer on average than that of the columnar-lined oesophagus control group, although it is possible that adenocarcinoma had completely overgrown shorter segments of columnar-lined oesophagus[184]. A number of studies following columnar-lined oesophagus cohorts have demonstrated that adenocarcinoma only developed in patients with long (≥3cm) segments[87-89]. The proportion of patients with dysplasia in the metaplastic segment has been reported as higher in longer segments than short segments[251;258]. However, both dysplasia and adenocarcinoma do develop in short (<3cm) segments of columnar-lined oesophagus[196;253], despite the fact that the severity of oesophageal injury as assessed by oesophageal acid and bile exposure and symptom frequency are lower in short than long segment columnar-lined oesophagus[66].

Only one study has stratified adenocarcinoma risk by segment length. Rudolph *et al.*[90] grouped patients into segment lengths <3cm, 3-6cm, 7-10cm and >10cm. They did not demonstrate any statistically significant difference in adenocarcinoma incidence in the

different segment length groups, but there was a trend for higher adenocarcinoma incidence in longer segment lengths.

Changes in Segment Length Over Time

Several studies have demonstrated that the length of columnarised segment increases[168;259;260] and decreases[134;153;198;219;259-268] or develops areas of squamous re-epithelialisation[153;261;269] in a proportion of patients over time. However, neither acid suppression medication nor antireflux surgery has demonstrated a reliable reduction in the length of the metaplastic segment; and overall, the segment length involved develops early[215] and does not change in time[111;199;215;270].

All studies of progression or regression observations on the metaplastic segment are dependent on accurate measurement of segment length. Peters *et al.*[198] examined the difference between observations of segment length 3 months apart as part of a study on segment length change with treatment, and stated that the standard deviation as a fraction of the mean measured length was 5%. Kim *et al.*[197] examined the proximal and distal extents of the columnarised segment and showed that the average position was consistent at endoscopies 6 weeks apart. However, 9% of patients had a change in the endoscopically determined gastro-oesophageal junction level of ≥4cm and only 46% of patients had the same level of proximal columnar-lined oesophagus extent determined endoscopically and histologically. Dekel *et al.*[199] stated that the mean intra-observer difference in segment lengths (measured to the nearest 0.5cm) was 1.6cm, and interobserver difference was 1.4cm. They noted that the differences tend to increase with increasing segment length. Guda *et al.*[200] examined inter- and intra-observer variability in the measurement of a model of an oesophagus with plastic inserts representing the columnarised segment. They found that the mean difference between the measured length and actual length was 1.1cm. When observers repeated their own measurements (later in the experiment), the intra-observer agreement of both measurements being between 0.5cm of each other was 0.40 (fair agreement) and 60% of the time observers tended to consistently over- or underestimate the true segment length.

Studies have also attempted to quantify the area of metaplastic mucosa to enable changes in the mucosa within the metaplastic segment (typically involving the re-growth of squamous islands within the columnar mucosa) to be taken into account when examining changes in

the total amount of metaplastic epithelium. Peters *et al.*[198] drew the outline of the columnarised segment on graph paper and estimated area by counting squares within the constructed diagram. Kim *et al.*[271] reconstructed a model of the columnarised segment using sequential digital photographs taken throughout the oesophagus, and found very high reproducibility between observers and a very low variation in the calculated area, which on average did not vary significantly on a subsequent measurement[272]. They also noted that on occasion (9/17, 53%) the segment length appeared to increase or decrease by ≥5%, but the estimated area would change discordantly. Eisen *et al.*[255] mapped the whole area of columnarised segment and proximal squamous epithelium with toluidine blue staining, photography and 4-quadrant biopsies, and found that at 30-60 days later, the epithelial type (intestinal/gastric/squamous/indefinite for dysplasia/low-grade dysplasia/high-grade dysplasia) was the same at both sets of biopsies at 94% of sites. These methods are time consuming and not appropriate outside of the research setting.

Dysplasia and Adenocarcinoma Risk

As discussed earlier, the epithelial subtypes in segments of metaplastic columnar-lined oesophagus are not homogenous and significant sampling error is encountered examining for intestinal metaplasia, dysplasia and superficial adenocarcinoma[273]. In addition, the grading of dysplasia by histopathologists is subject to significant variation, and is discussed below. Dysplasia has been demonstrated surrounding adenocarcinoma in resected specimens in the majority of cases (26/26[49], 26/28[185] and 7/9[184] had high-grade dysplasia surrounding the adenocarcinoma).

Some series of follow-up of columnar-lined oesophagus have shown that adenocarcinoma only develops in patients who previously demonstrated dysplasia[92-94]; and in one, all patients who developed adenocarcinoma had previously shown high-grade dysplasia[93].

Skacel *et al.*[95] demonstrated that 7 of 25 patients with a diagnosis of low-grade dysplasia developed high-grade dysplasia or adenocarcinoma at a mean follow-up of 26 months (annual incidence 12.9%), and the risk was higher in patients where there was a higher level of agreement between histopathologists.

Reid *et al.*[47] reported that 3 of 43 patients with low-grade dysplasia developed adenocarcinoma (annual incidence 12%). All of the patients who developed adenocarcinoma had aneuploidy, or an increased 4N fraction on flow cytometry.

High-Grade Dysplasia

Pellegrini and Pohl[96] reviewed the literature between 1983-1999 and found 15 studies examining the frequency of adenocarcinoma in patients operated on for high-grade dysplasia. The frequency varied from 0-73%, but overall 80/184 (43%) patients had at least a focus of adenocarcinoma in the resected specimen. Subsequent studies have shown an adenocarcinoma prevalence in oesophagectomy specimens resected for high-grade dysplasia in columnar-lined oesophagus of 5/15 (33%)[274] and that a 4-quadrant biopsy every 2 cm protocol would miss 13/26 (50%) of adenocarcinomata detected by a 4-quadrant 1cm protocol[275].

Since that study, 2 studies have examined whether the extent of high-grade dysplasia correlates with the probability of discovery of an occult carcinoma in the resected oesophagus. Buttar *et al.* from the Mayo Clinic (Minnesota, USA)[97] defined the extent of high-grade dysplasia of 100 patients into focal (≤5 crypts and acini involved in one biopsy specimen only) and diffuse (>5 crypts or multiple biopsy areas involved). They found a significantly higher risk with diffuse high-grade dysplasia (p=0.02 on multivariate analysis, relative risk 3.7) in developing adenocarcinoma at both 1 year (7% in focal high-grade dysplasia, 38% in diffuse) and 3 years (14% and 56% respectively).

Dar *et al.*[276] from the Cleveland Clinic (Ohio, USA) defined focal involvement as high-grade dysplasia at only one level at which biopsies had been taken, and diffuse as involvement at multiple levels. Although they found a trend for an increased proportion of occult adenocarcinoma in patients with diffuse high-grade dysplasia (14/21, 67%) compared with focal high-grade dysplasia (10/21, 48%), this did not reach statistical significance (p=0.35), and when they applied the Mayo Clinic criteria, the trend was less apparent.

Even if adenocarcinoma is not present synchronously when high-grade dysplasia is diagnosed, there is a significant risk of it developing subsequently. Schnell *et al.*[277] followed-up 79 patients with high-grade dysplasia for 7.3 years, during which time the adenocarcinoma incidence was 2.2% in the first year and 2.1% per annum overall. All of the adenocarcinomata which developed were detected at a curable stage (with the exception of one in a patient who had defaulted follow-up). They concluded that their 3 monthly surveillance protocol detected adenocarcinoma at a curable stage, and did not recommend oesophagectomy for high-grade dysplasia alone. Buttar *et al.*[97] found that overall 27.8% of

patients in their cohort of 100 patients with high-grade dysplasia developed adenocarcinoma in the first year, and that the annual adenocarcinoma incidence over the first 3 years was 14.0%. Romagnoli *et al.*[278] studied patients with high-grade dysplasia categorized into 3 groups: patients operated on immediately after the diagnosis, patients whose high-grade dysplasia persisted or progressed to adenocarcinoma at 6 months (and underwent oesophagectomy at that point) and the third group of patients who only underwent oesophagectomy when they had symptoms of dysphagia or biopsies demonstrated adenocarcinoma after 6 months (after high-grade dysplasia had been initially diagnosed). They demonstrated that the cancer-related survival was 100% in those operated-on immediately, but only 52.5% in those surveyed for 6 months or more, and advised oesophagectomy as the treatment of choice in high-grade dysplasia. Rudolph *et al.*[90] showed that the annual incidence of adenocarcinoma in patients with high-grade dysplasia was 23.0%, compared to 0.8% in patients without high-grade dysplasia at diagnosis.

The current UK guidelines on the management of oesophageal and gastric cancers recommend that in the case of high-grade dysplasia - urgent review of endoscopy with repeat biopsy is undertaken, then careful consideration should be given to resection[279].

Interobserver Agreement in Grading of Dysplasia

Reid *et al.* in 1988[280] demonstrated that the interobserver agreement between 8 histopathologists when comparing the grouped diagnoses of columnar-lined oesophagus with no dysplasia, indefinite for dysplasia and low-grade dysplasia to the diagnoses of high-grade dysplasia and adenocarcinoma was 85% and 87% on successive reviews of slides. They concluded that experienced gastrointestinal pathologists could diagnose high-grade dysplasia and adenocarcinoma with a high degree of agreement and consequently detect which patients needed immediate re-biopsy or surgical resection.

The Vienna histopathology guidelines on the grading of dysplasia throughout the alimentary tract were published in 2000[189]. They demonstrated that the kappa coefficient for interobserver agreement between 31 histopathologists on grading of dysplasia (into the categories listed above) on 21 oesophageal slides was 0.01 (agreement of 14%) prior to the agreement of the classification system and was 0.31 (agreement of 62%) after the classification meeting. The interobserver agreement on oesophageal dysplasia was more

variable than that of stomach or colorectal pathology slides, and was least variable at the ends of the spectrum of dysplasia. In a study examining the outcome of low-grade dysplasia, the interobserver agreement between 3 pathologists for the diagnosis of low-grade dysplasia kappa value was 0.17 (poor agreement, actual agreement 45.7%)[95]. Montgomery *et al.*[281] reported the intra- and interobserver agreement of 12 gastrointestinal pathologists on 250 slides of columnar-lined oesophagus before and after a consensus meeting with a multi-headed microscope and categorised them into the same two groups as Reid *et al.* above[280] as well as sub classifying the slides further. They found intra-observer agreement was almost perfect both before (kappa=0.82) and after (kappa=0.80) a consensus meeting. Interobserver variability was substantial both before (kappa=0.66) and after (kappa=0.70) the consensus meeting and had improved following the meeting (p=0.02). When separating the pathological diagnoses into 4 groups (no dysplasia, indefinite for dysplasia, low-grade dysplasia and the fourth group: high-grade dysplasia and adenocarcinoma together), the intra-observer agreement was substantial before (kappa=0.60) and after (kappa=0.65) the consensus meeting and interobserver agreement was moderate both pre- and post the consensus meeting (kappa=0.43 pre- and post-meeting). They also stated that the agreement was highest at the ends of the histological spectrum, and poorest for the middle of the spectrum (kappa values for: no dysplasia 0.44, indefinite for dysplasia 0.14, low-grade dysplasia 0.23, high-grade dysplasia 0.40, adenocarcinoma 0.67).

Ormsby *et al.*[282] examined interobserver agreement between 2 gastrointestinal pathologists and one general pathologist on the diagnoses of high-grade dysplasia, intramucosal adenocarcinoma and invasive adenocarcinoma. They found that the overall agreement for these diagnoses was fair (kappa=0.59) and between the gastrointestinal pathologists agreement was good (kappa=0.68). Comparing high-grade dysplasia to intramucosal adenocarcinoma, the agreement between all pathologists was fair (kappa=0.42) and between gastrointestinal pathologists was also fair (kappa=0.56). Comparing high-grade dysplasia to submucosal adenocarcinoma (the stage at which tumour spread to involve lymph nodes occurs much more frequently[71] necessitating a more radical approach to resection than treatment of the mucosa only) was perfect (kappa=1.00) between all pathologists, and comparing intramucosal adenocarcinoma to submucosal carcinoma: agreement was good between all pathologists (kappa=0.71) and gastrointestinal pathologists (kappa=0.76).

Mucosal Abnormalities and Adenocarcinoma Risk

The relative risk of patients with high-grade dysplasia and a mucosal abnormality (nodule) of developing adenocarcinoma was nearly 4x those whose mucosa did not have focal lesions apparent to the examining endoscope[97], and presence of ulcers has also been associated with a higher adenocarcinoma risk[111].

Medical and Surgical Treatment of Columnar-Lined Oesophagus

The American College of Gastroenterology states that: "*the goals of therapy of Barrett's Esophagus are the same as for [gastro-oesophageal reflux disease]: the control of symptoms of [gastro-oesophageal reflux disease] and the maintenance of a healed mucosa*"[91].

The mainstay of treatment is with proton pump inhibitors, often required in high doses (due to the severity of the gastro-oesophageal reflux[65;123]) and with administration twice-per-day[124]. Proton pump inhibitors are effective at neutralising the pH of the acidic reflux[125] and also reducing the volume of the refluxate[65;125], however they neither protect the oesophagus from the reflux of bile and pancreatic secretions (as measured by bilitec)[65;126] nor prevent the development of oesophageal columnar metaplasia in gastro-oesophageal reflux disease, even once reflux oesophagitis and symptoms have been abolished[127;128]. However, many patients are still symptomatic despite high-dose therapy[129] and up to 40% of patients who are rendered symptom-free on up to 80mg daily of Omeprazole still have pathological acid exposure[124;129;130].

Surgical treatment produces a physical barrier to all components of gastro-oesophageal reflux[283]. Surgical procedures generally consist of reducing (and anchoring) the hiatal hernia below the diaphragm and reconstruction of the lower oesophageal sphincter (often using a fundoplication and tightening of the diaphragmatic crura) and may be done by a variety of techniques[284-288]. Post-operative studies have shown that antireflux surgery is effective, both in controlling reflux symptoms[289] and on physiological testing of oesophageal acid and bile exposure[131-135]. However, concerns remain that the long-term failure rate[133;138] may overcome the apparent early benefits.

The American College of Gastroenterology guidelines state that: "*as a group, patients with Barrett's have a greater esophageal acid exposure than other GERD patients, and control of symptoms may require higher than usual doses of proton pump inhibitors ... Patients who are appropriate surgical candidates may elect antireflux surgery*"[91].

Several small series have suggested that surgery may confer a protective effect against adenocarcinoma development[129;134;219], and two large meta-analyses have been published on this subject[136;137](table 2.T1).

Bammer *et al.*[136] reviewed the literature between 1977-99 and found 40 studies on columnar-lined oesophagus treatment and outcome. They found a trend for a lower adenocarcinoma incidence in patients treated surgically and concluded that surgery was cost effective at 7 years compared to medical therapy (allowing for 20-40% of surgical patients continuing to take antireflux medication). They suggested that "*surgery may be superior to medical treatment to prevent progression of Barrett esophagus and the development of carcinoma*".

Corey *et al.*[137] reviewed 34 studies in the literature between 1966-2001. Their results were similar to Bammer *et al.*[136], however, they conclude that "*surgical antireflux procedures do not seem to provide benefit over medical therapy in Barrett's esophagus in reducing the incidence of cancer development. Surgical antireflux procedures should not be recommended over medical therapy to decrease the cancer risk associated with Barrett's esophagus*".

Table 2.T1 – Results of Meta-Analyses Comparing Medical to Surgical Therapy for Columnar-Lined Oesophagus

Study	Treatment	No. Studies	No. Pts	Total FU	No. AC	AC Incidence
Bammer *et al.*[136]	Medical	21	669	2026.3	14	1/144.7
	Surgical	19	902	4121.7	14	1/294.4
Corey *et al.*[137]	Medical	24*	918	4906.2	26	1/188.7†
	Surgical	19*	754	4678.3	18	1/259.9†

* 9 studies had both medical and surgical arms
† p=0.29

Symptoms and Oesophageal Columnar Metaplasia, Dysplasia and Adenocarcinoma

When Barrett described columnar lining of the thoracic oesophagus, he noted that there was a strong association of the metaplastic lining with symptoms of heartburn[41]. The proportion of the general population with reflux symptoms is very high (29% of a US householder survey[206]), and specific symptoms of heartburn and acid regurgitation have been shown to be sensitive predictors of gastro-oesophageal reflux disease, but with poor specificity for this condition. The duration of symptoms has been correlated with the length of the metaplastic segment in patients with columnar-lined oesophagus[290] and patients with metaplastic changes have a longer duration of symptoms compared to patients with reflux oesophagitis[67]. Patients with intestinal metaplasia had longer duration of symptoms compared to those with columnar-lined oesophagus without intestinal metaplasia[250], but others studies have not shown such an association with segment length or demonstrable difference between columnar metaplasia and simple inflammation[203;290]. The frequency of symptoms has also been shown to be higher in patients with oesophageal columnar metaplasia than patients with reflux oesophagitis in some studies[154;224;227;248], but this difference has not been demonstrated by all studies[67]. The major symptoms at diagnosis of columnar lined oesophagus reported by most patients are heartburn and acid regurgitation[82;203;221;222;224], but patients may also present with dysphagia (often secondary to a benign oesophageal stricture)[82;203;221;289], upper gastrointestinal bleeding or anaemia[203;221;222] and various other gastrointestinal or general symptoms[203;222]. A minority of patients are diagnosed at follow-up endoscopy for other upper alimentary conditions[203;222] and up to 19% have no upper gastrointestinal symptoms at

diagnosis[82;221;290]. Although the classical symptoms of gastro-oesophageal reflux are those most closely associated with oesophageal columnar metaplasia[224], in many studies there is no clear distinction in the specific types of symptoms and probability of the finding of oesophageal columnar metaplasia rather than simple reflux oesophagitis[203;289] demonstrating that these are part of the same disease spectrum[121]. The presence of nocturnal reflux symptoms has not been correlated with the development of oesophageal columnar metaplasia[224] (unlike adenocarcinoma).

Lagergren *at al.*[39] demonstrated the association between symptoms of long-standing gastro-oesophageal reflux and oesophageal adenocarcinoma. The odds ratio for the most frequent symptoms (3x per week compared to no reflux symptoms) was 16.7, for the most severe symptoms (compared to no reflux symptoms) was 20.0 and for the longest duration of symptoms (more than 20 years) was 16.4. The presence of night symptoms was associated with a risk ratio of nearly 11, and overall, patients with the longest duration, most severe and frequent symptoms had an overall odds ratio of 43.5. The major symptom of oesophageal adenocarcinoma is dysphagia[69;221;291;292], but reflux[186;187], weight loss[69;291;292], upper gastrointestinal bleeding or anaemia[69;291;292], chest pain[221], nausea and vomiting[292] and dyspepsia[222] have also been correlated with the development of dysplasia and the presence of reflux symptoms has been correlated with physiological findings of pathological acid and bile reflux[186].

Treatment of High-Grade Dysplasia and Adenocarcinoma

Treatment of high-grade dysplasia aims to remove the neoplastic (or dysplastic) tissue, whilst minimising morbidity to the patient. Treatment modalities are: endoluminal resection, endoluminal ablation (photodynamic therapy, laser thermal ablation and multipolar electrocoagulation), radiotherapy, surgical resection or systemic chemotherapy. Palliative treatment for adenocarcinoma includes stenting and laser photocoagulation. Despite the increase in oesophageal adenocarcinoma, increasing numbers of these neoplasms (as well as the proportion of patients as a total of all oesophageal adenocarcinomata) are being detected at earlier stages, which enables radical treatment (aimed at cure rather than palliation) to be undertaken[107-109]. However, one third or more of patients have metastatic disease at presentation, only one third overall undergo resection[8] and 90% still die as a consequence of their disease[69].

Principles of Treatment of High-Grade Dysplasia and Adenocarcinoma

Definitive treatment of oesophageal malignancy should involve wide excision of the diseased segment with associated soft tissue and lymphovascular structures to ensure local clearance and allow full histopathological assessment of the tumour and presence of lymphatic spread[71;110-112]. Due to the multifocal nature of dysplasia and neoplasia within the segment and potential for metachronous lesions to develop in time[116;293;294], treatment should be aimed at removal of the entire metaplastic mucosal segment[108;293;294]. However, the morbidity and mortality associated with thoracoabdominal oesophagectomy[71;110-112;291] in this older patient group has driven research into less invasive therapies. These therapies may be appropriate for the most superficial lesions (when risk of lymphovascular invasion is very low), or in patients who are unfit for oesophagectomy.

Staging of Oesophageal Adenocarcinoma

The Association of Upper Gastrointestinal Surgeons of Great Britain and Northern Ireland, British Society of Gastroenterology and British Association of Surgical Oncology guidelines for the management of oesophageal and gastric cancer[279] state that

"*Accurate staging of oesophageal tumours is essential to allow a well informed decision to plan appropriate treatment*".

Staging for oesophageal adenocarcinoma (after histological confirmation) should involve spiral computed tomography (CT) with 5mm (or less) slices. CT is inferior to endoscopic ultrasound in the evaluation of local tumour extension (T stage) and local nodal involvement (although its specificity for local nodal involvement is good[279]), but is useful for the diagnosis of distant metastases. Endoscopic ultrasound (EUS) is the most reliable modality for locoregional staging, with an accuracy in primary tumour staging of 84-87% and nodal staging 77-91% (based on four typical features: well defined margins, ≥1cm diameter, rounded and hypoechoic)[279;295-299].
Positron emission tomography (PET) has good specificity (84-100%), but lower sensitivity (38-77%) for the detection of nodal and metastatic disease[300-303].

At initial presentation, 147 of 838 patients had metastatic disease[70], and the majority (69%) of these were detected on CT scanning of the thorax and abdomen. The remainder were detected on bone scan (6%), physical examination (3%), head CT (2%), chest radiograph (2%), bone radiograph (1%) and 25% were only discovered at surgery.

The Association of Upper Gastrointestinal Surgeons of Great Britain and Northern Ireland, British Society of Gastroenterology and British Association of Surgical Oncology recommend that all patients should undergo CT and (in the absence of clear metastases) EUS. Further modalities and techniques which should be available in selected cases include chest radiography, transabdominal ultrasound, magnetic resonance imaging, bronchoscopy and laparoscopy[279].

Primary Tumour Invasion and Probability of Lymphatic Spread and Metastasis

To assess the spread of oesophageal adenocarcinoma to lymph nodes, several studies have examined the histology of resected oesophagectomy specimens, classifying tumours by their depth of invasion[304]. Holscher *et al.*[110] demonstrated that none of the patients with oesophageal adenocarcinoma they had resected for intramucosal lesions (T1a) had lymphatic spread, compared to 18% of patients with submucosal involvement (T1b). Patients with tumour involving the muscularis propria (T2) had lymph node involvement in 77% of cases, patients with tumour spread into the adventitia (T3) had lymph node involvement in 83% of cases and those with spread through the adventitia to involve adjacent structures (T4) had lymph node involvement in 96% of cases. Hagen *et al.*[71] demonstrated that in 100 consecutive oesophagectomy specimens for adenocarcinoma of the oesophagus, only one of sixteen (6.3%) with T1a tumours (adenocarcinoma confined to the mucosa) had lymph node metastases, compared to five of sixteen (31.3%) of patients with T1b lesions (adenocarcinoma invasion into the submucosa), 10/13 (76.9%) of patients with invasion to the muscularis propria (T2) and 47/55 (85.5%) of tumours spreading through the muscularis propria to the adventitia (T3). The probability of distal node involvement (which would not be resected by more limited surgical approaches) also increased with higher tumour stage. Studying T1 lesions, Stein *et al.*[108] found lymph node metastases in 0/38 patients with T1a lesions, and 10/56 (17.8%) with T1b lesions.

The pattern of early metastases detected by positron emission tomography was liver (27 of 100 scans), lung (7 of 100 scans), bone (3 of 100 scans), adrenal (1 of 100 scans), chest wall (1 of 100 scans) and distant lymph nodes (16 of 100 scans). In a series of 838 patients presenting to the University of Michigan with oesophageal cancers over a 12 year period, 147 had metastatic (M1) disease. Of the 105 patients with adenocarcinoma and metastases, the site(s) of metastatic disease were: liver (45%), abdominal lymph nodes (42%), lung (19%), cervical lymph nodes (13%), bone (10%), adrenal (7%), peritoneum (3%), brain (2%), pleura (2%), skin (2%), pericardium (1%) and spleen (1%)[70].

Surgical Resection

Surgical resection is still the mainstay of definitive treatment of oesophageal adenocarcinoma, however the high peri-operative mortality and morbidity associated with the procedures have prompted research into less invasive techniques for treatment of high-grade dysplasia and early cancers, and resection is only usually undertaken with curative intent[279]. Tumours may theoretically be resectable if they are T1-T3, N0-N1 and the coeliac nodes may also be cleared at resection (involvement signifies M1a disease, but 5-year survival when these nodes are involved is very poor[305]). A two-stage Ivor-Lewis oesophagectomy (laparotomy and construction of a gastric tube followed by a right thoracotomy) allows a more extensive mediastinal lymphadenectomy than a transhiatal approach. Left-sided thoracoabdominal approaches are also used for some tumours and a third cervical phase may also be added to allow resection of lesions extending proximally and construction of an anastomosis in the neck rather than the mediastinum. An extensive resection (at least 5cm beyond the macroscopic limits of the tumour) is also recommended to prevent involvement of resection margins[279], and – as stated above – resection should also remove the entirety of the metaplastic segment. Lymphadenectomy will involve the abdominal (right and left gastric cardiac node, lesser curve nodes and hepatic artery, splenic artery and left gastric artery nodes) and mediastinal (para-aortic nodes and thoracic duct, para-oesophageal nodes, bilateral pulmonary hilar nodes and carinal nodes) compartments. A third stage lymphadenectomy involves removal of nodes from the cervical compartment, but is not recommended for adenocarcinoma of the oesophagus[279]. The choice of conduit is generally gastric tube or colonic interposition graft, although small bowel may also be used[279].

Morbidity of Oesophageal Resection

The complication rate following 3-stage oesophagectomy is very high (71%) and similar between patients who had a colonic interposition and gastric pull-up[71]. Following transhiatal oesophagectomy (for T1 tumours) with cervical or high thoracic anastomosis, the complication rate is 43.7%[108]. In patients who have undergone limited oesophagectomy with jejunal interposition, the complication rate is lower at 20.8%, and at one year post-operation, quality of life was similar to control subjects and patients at six weeks following cholecystectomy and fundoplication[108]. Overall post-operative complication rates are typically around 40%[107;108].

Endoluminal Ablation

Endoluminal ablation of the columnar segment may be undertaken using thermal or photodynamic modalities. Thermal therapies destroy the surface of the oesophagus using heat by means of argon plasma coagulation, heat probe and Nd:YAG laser. Reversal of the metaplastic epithelium by argon plasma coagulation has been reported in 38-98% of patients[113;114], but underlying intestinal metaplasia in the neosquamous epithelium has been reported in up to 30% of patients[114;306]. Strictures[306] and perforation[306] may also occur following treatment. Photodynamic therapy involves administration of a photosensitising agent, which is taken up preferentially by the metaplastic and dysplastic epithelium. The photosensitising agent is activated by a specific light wavelength, and produces oxygen radicals, destroying the tissue involved. Overholt *et al.*[115] reported that following treatment of 101 patients, 54% had no residual columnar metaplasia, and successful elimination of low-grade dysplasia, high-grade dysplasia and cancer were 93%, 78% and 44% respectively. Their overall stricture rate was 30%. Endoluminal ablation does not allow any histopathological assessment of the treated tissue until mucosal healing has commenced, and no specimen is available for evaluation of depth of tissue invasion and involvement of treated margins.

Endoluminal Resection

Endoluminal resection may be undertaken by needle knife, insulated-tip knife or suction and snare. With small lesions (diameter 2cm or less) of early adenocarcinoma (T1), complete reversal of cancer has been demonstrated in 97% of patients following a mean of 1.3 treatments[116]. However a recurrence or metachronous cancer developed in 17% of patients at one year of follow-up. Histopathological examination of the resected specimen allows accurate staging of the depth of invasion[307].

To reduce the risk of recurrent and metachronous adenocarcinoma or high-grade dysplasia, multimodal therapy involving endoscopic mucosal resection followed by ablative therapies have been used[293;294].

Adjuvant Therapy

There have not been any studies demonstrating a benefit from adjuvant chemotherapy for adenocarcinoma of the oesophagus.

Neoadjuvant Therapy

Neoadjuvant therapy may lead to downsizing of the primary tumour (and increase the probability of a complete resection), and also is the earliest means of treating metastatic spread of malignant cells[296;308]. There have been two landmark trials of neoadjuvant chemotherapy compared to surgery alone for oesophageal adenocarcinoma. The US Intergroup study[309] randomised 440 patients with T1-T3 N0-N1 M0 tumours (squamous cell carcinomata and adenocarcinomata) to three cycles of cisplatin and 5-fluorouracil followed by surgery and 2 further cycles of chemotherapy or surgery alone. They reported similar proportions of pathological complete resections, peri-operative mortality and complication rates between the two arms of the study. Overall and disease-free survival were similar between the two groups, with median survival 14.9 months in the neoadjuvant group and 16.1 months in the surgery alone group (no statistical difference). The survival was also similar between squamous cell carcinomata and adenocarcinomata, and for patients who had pathological complete resections in the two arms. The UK Molecular Research Council OE02 study[310] randomised 802 patients with squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma of the oesophagus to 2 cycles of cisplatin (at a lower dose than the Intergroup study[309]) and 5-fluorouracil (at a lower dose than the

Intergroup study[309]) followed by the surgeon's choice of resection or surgery alone (surgeon's choice of procedure). They reported an improved survival in the neoadjuvant group: median survival of 512 days, surgery only group median survival of 405 days (21% reduction in risk of mortality). Complete pathological resections and post-operative complications were similar between the two groups. The benefit of neoadjuvant chemotherapy demonstrated by the OE02 study[310] may be due to lower toxicity of the chemotherapy, shorter delay to surgery following chemotherapy and a higher proportion of the OE02 neoadjuvant arm undergoing resection than in the Intergroup trial[309]. The Molecular Research Council OE05 study is underway (aiming for 1300 patients with oesophageal adenocarcinoma) comparing 4 cycles of epirubicin, cisplatin and to 2 cycles of cisplatin and 5-fluorouracil (as in OE02[310]) followed by Ivor Lewis oesophagectomy to standardise surgical treatment, and will examine overall and disease-free survival with quality of life as a secondary outcome measure.

Other studies have examined the use of neoadjuvant chemoradiotherapy compared to surgery alone in the treatment of oesophageal adenocarcinoma[296;311;312], but no survival benefit has been demonstrated in a randomised study, except in one study which did not have evenly matched groups at entry into the study[312]. A meta-analysis of 9 randomised controlled trials for treatment of oesophageal squamous cell carcinoma and adenocarcinoma demonstrated that overall there is a tendency for neoadjuvant chemoradiation to be superior to surgery alone when examining overall 3-year survival[313]. Although patients who had undergone neoadjuvant chemoradiation were less likely to undergo a resection than the surgery only patients, their resection margins were more likely to be free of tumour involvement. Despite the lack of objective evidence that neoadjuvant chemoradiation improves survival, some patients are reported to have pathological downstaging of their tumours in the resected specimen (to the point where in a minority of patients a complete pathological response occurs – no residual tumour can be demonstrated) compared to their pre-operative clinical staging[296;297;311] and these patients have an improved survival compared to those whose tumours are not downstaged by chemoradiation[297;298;311].

Palliative Treatment

Dysphagia is the predominant symptom in advanced oesophageal cancer[279], and effective palliation of swallowing correlates strongly with quality of life[314]. Palliative treatment may involve systemic chemotherapy (if the patient is well enough) typically with cisplatin and 5-fluorouracil; and is associated with both an improvement in survival and dysphagia symptoms[315-318]. Chemotherapy may be used alone or in combination with other treatment modalities. Local treatment with radiotherapy, brachytherapy and endoscopic treatments including stenting, injection, dilatation and laser photocoagulation are also used to palliate symptoms[69;279].

Pattern of Recurrence

Local recurrence following en-bloc resection for oesophageal adenocarcinoma with no residual tumour by 3-stage oesophagectomy with stomach pull-up or colonic interposition is very low 1%[71] and the median time from resection to systemic recurrence is 10-11 months[71;319]. Distant recurrence occurs more frequently with increasing tumour depth of invasion (0% T1a, 17% T1b, 25% T2, 60% T3[71])[319], nodal involvement[108] (0% of N0, 57% of N1[71]), number of nodes involved[71;319], tumour differentiation[319] and ratio of number of nodes involved to total number of nodes resected[71]. Three of 13 patients with recurrence of adenocarcinoma in a series of 122 patients with high-grade dysplasia, T1a or T1b adenocarcinomata treated by transhiatal or transthoracic oesophagectomy were due to locoregional recurrence and 10 from distant metastases[109]. Recurrence following oesophagectomy in 176 patients with adenocarcinoma (113 patients) or squamous cell carcinoma of the oesophagus treated by Ivor Lewis oesophagectomy with two-field lymphadenectomy was locoregional in 27% and distant in 18%[319].

Survival

The perioperative mortality following 3-stage oesophagectomy was 6%[71]. Perioperative mortality for early stage (T1) adenocarcinomata treated by transhiatal oesophagectomy and high thoracic or cervical anastomosis was 4.2%[108] and for Ivor Lewis oesophagectomy was 3.8%[106]. Perioperative mortality following transhiatal limited oesophagectomy for short

segment (<3cm) of columnar metaplasia with early tumours (T1-T2) was 0 in 24 patients, and there was no mortality at a median of 15 months of follow-up[108]. The Cleveland Clinic reported a perioperative mortality of 3 of 122 (2.5%) patients with high-grade dysplasia, T1a or T1b adenocarcinoma treated by transhiatal or transthoracic oesophagectomy[109].

The 5-year survival of patients following 3-stage oesophagectomy by tumour stage is 100% for T1a, 72.9% for T1b, 85.7% for T2, and 30.5% for T3; for nodal stage it is 91.6% for N0, 35.5% for N1[71]. For patients who have undergone neoadjuvant treatment with pathological downstaging from N1 to N0, the 5-year survival was 37%, compared to 12% in patients whose tumours had not been downstaged by the treatment. Patients who had undergone neoadjuvant chemotherapy for clinical N0 disease which pathologically was also N0 had similar 5 year survival to the patients downstaged at 35%, and patients who had clinically been staged as N0 but had nodal involvement in their resected specimens after neoadjuvant chemoradiation did not survive to 5 years from study entry[297]. Examining patients with high-grade dysplasia, T1a and T1b adenocarcinomata treated by transhiatal oesophagectomy, Rice *et al.*[109] found that the overall 5 year survival was 77%. Of the 19 deaths (from the total cohort of 122 patients), 13 were due to cancer recurrence. The strongest predictors of mortality are tumour stage, nodal involvement, patient age, weight loss, residual tumour at resection and respiratory failure post-operatively requiring re-intubation[107;109]. Ruol *et al.*[106] state that the 5-year survival of their cohort of patients with T1 adenocarcinoma treated by Ivor Lewis oesophagectomy was 83%.

Summary and Purpose of This Study

Adenocarcinoma of the oesophagus is clearly an escalating issue especially in Western Countries. Its association with long-standing gastro-oesophageal reflux and metaplastic columnar-lined oesophagus, frequently with preceding or concurrent dysplasia is well-established. The patient groups at highest risk of adenocarcinoma development, optimum screening and surveillance practice and most effective preventative management are poorly defined. This study seeks to elucidate the natural history of columnar-lined oesophagus, identifying which patients are at greatest neoplastic risk and which therapeutic interventions minimise risk.

Chapter 3 - Methodology

Introduction

The UK National Barrett's Oesophagus Registry

The UK National Barrett's Oesophagus Registry was founded in 1996 as a joint venture between the Oesophageal Section of the British Society of Gastroenterology and the Upper Digestive Tract Group of the European Cancer Prevention Organisation[139]. Its objective was to initially form a register of patients throughout the United Kingdom who had been diagnosed with Barrett's columnar-lined oesophagus. Once the register had been established, it would be used to examine:

1. Prevalence of diagnosed cases of Barrett's oesophagus
2. Regional variations of Barrett's oesophagus in the UK
3. Variation of prevalence of Barrett's oesophagus with time
4. Natural history of the disease and influence of treatment
5. The incidence of adenocarcinoma in Barrett's oesophagus
6. Which factors influence neoplastic transformation

Its final objective was to provide a central resource and co-ordinating infrastructure for prospective studies.

Contact was made with registrants following introductions made at national and international gastroenterology meetings. Six consultants were approached "cold" by mail, without a previous introduction; however, none of them replied or commenced registration, and so no further attempts at "cold" registrations were made.

The registry contains patient data on name, gender, date of birth, date of diagnosis and consequently age at diagnosis. This basic demographic data constituted "form 1", and was published with the first results from the registry in 1998[74]. This data enabled the first 3 objectives above to be studied. In order to examine the natural history of the disease, transformation to adenocarcinoma and factors influencing the natural history and neoplastic

transformation, a second phase of the project was planned to examine patients' clinical records in depth and collect this data to complete "form 2" (see appendix 2).

At commencement of this project, 7,500 patients had been registered from 37 centres. At the completion of data acquisition of this project, 48 centres had actively registered patients and 38 centres, who had agreed to register patients, had not done so.

Following the success of UKBOR, the registry co-directors and registrar have advised other small European registries on their setting up and day-to-day running (with the result of successful regional registries operating in Italy, Germany, Czech Republic and Poland).

"The Natural History Study"

"The natural history study" was undertaken from 11th April 1996, with the final data collection terminating on 15th September 2004. The project was funded by a grant from the Wexham Gastrointestinal Trust.
This research project was devised with 3 specific hypotheses (based on the original UKBOR objectives):

1. That the natural history (length, histology and development of complications) of the columnarised segment changes with time
2. That pharmacological, surgical and endoscopic therapy influence the natural history to differing extents
3. That characteristics of Barrett's oesophagus patients at greatest risk of adenocarcinoma can be defined

The study involved collection of data exclusively from hospital medical records, and any up-dated patient information sent from the registering centres either in addition to "form 2" data, or on patients who had been registered, but had not had "form 2" completed. This (latter) data usually took the form of endoscopic and histological reports, reports of patient death or letters from the gastroenterology or general surgical department. There was no direct patient contact initiated from UKBOR, and no information was sought from general practitioners or other healthcare services in accordance with the ethics committee permission statement.

Ethical Permission for Study

Approval for this study was granted by the London Multi-Centre Research Ethics Committee on 14th March 2002, number MREC/02/26.

Data Collection

The number of patients required for the study was calculated using the formula for binary outcomes in groups[320]. The value for accepted statistical power 1-β is 80% and statistical significance was set at 1-α of 95%

$$m = \frac{\{(z_1 - \frac{\alpha}{2})\sqrt{2p(1-p)} + (z_1 - \beta)\sqrt{pA(1-pA) + pB(1-pB)}\}^2}{\delta^2}$$

Where: m=number of patients in each arm of the study

z_1-α/2=1.96 (for 2-tailed test with probability of type I error α=5%)

z_1-β=0.84 (for statistical power of 1-β=80%)

pA=Proportion of group A developing condition

pB=Proportion of group B developing condition

p=pA/2+pB/2

δ=pA-pB

The values of m for various proportions developing the condition are shown below in table 3.T1.

Table 3.T1 – Power Calculation of Number of Patients Required in Each Arm of Study

Probability of Event in Group A	Probability of Event in Group B	No. in Each Group	Total Sample Size
0.1	0.05	434	868
0.1	0.025	162	324
0.1	0.01	99	199
0.05	0.025	904	1809
0.05	0.01	284	568
0.05	0.005	206	412
0.02	0.01	2316	4631
0.02	0.005	859	1718
0.02	0.0025	568	1137
0.01	0.005	4668	9335
0.01	0.0025	1730	3460
0.01	0.001	1057	2115

Consequently, a sample size of 2,500 patients was chosen, which would detect a 2-fold difference in the proportion of patients who developed adenocarcinoma split between 2 equally-sized groups with the proportion of events in the control group (A) of 5%, and group B 2.5% with probability of type I error of 5% and 80% power.

Seven centres were asked to participate in the natural history study. These centres were chosen to provide a broad cross-section of patients within Great Britain geographically and economically – 1 in Scotland, 1 in Wales, 1 in London, 2 in the Home Counties, 1 in North Yorkshire and 1 in South Yorkshire. These were also centres where the gastroenterology and/or general surgical departments were actively undertaking surveillance of columnar-lined oesophagus, and had registered >80 patients with UKBOR (see appendix 3).

Data acquisition and entry onto the database occurred in two phases:

1. Hand-searching of patients' hospital records and accrual of all "form 2" data
2. Data entry into the database from the information retrieved from hospital records

The medical records of patients who had had "form 1" completed were requested from medical records departments, and were examined manually by 3 registry researchers: Christine Caygill PhD (UKBOR Registrar), Piers Gatenby MA BM BCh MRCS (UKBOR

Research Fellow) and James Ramus BSc MBBS MRCS (UKBOR Research Fellow). Data were extracted and transcribed directly to "form 2" (see appendix 2), a basic template encompassing most of the information which would be inputted into the database, but sufficiently flexible to allow for differences in patients' treatment and management to be recorded without necessitating an excessively large form. Further data were acquired by photocopying pages from hospital records (when this would be faster than transcribing a large amount of data on to the "form 2" template by hand). Typically, the data photocopied included long lists of medications, endoscopic and histology records, operation notes, and discharge summaries and other data-rich correspondence.

Subjects were included in the database if they fulfilled the following criteria:

1. The registry had been supplied with a name, hospital number, gender and date of birth, and the centre registering the patient could be identified
2. A date of diagnosis of columnar lined oesophagus could be ascertained either from the registration data on form 1 or from data collected as form 2

The 7 centres which participated in the "natural history study" are listed in appendix 3. These patients were recruited between 11th April 1996 and 2nd February 2004. Overall, "form 2" data were available for 1651 (60.0%) of patients. Seven hundred and twenty five patients (26.4%) had some information available (e.g. endoscopy and histology reports), but insufficient data available (notes could not be found/were incomplete/had been destroyed). Three hundred and seventy five patients (13.6%) had no data available other than name, gender, date of birth and date of diagnosis. This final group of patients was kept on the database to allow them to be involved in the basic demographic calculations (gender ratio and age/date at diagnosis). The total number of patients on the database was 2751. The gender breakdown and median age at diagnosis were similar in patients who had "form 2" completed when compared to those who had not had "form 2" completed in each centre. In 5 of the centres, the median date of diagnosis of subjects for whom a "form 2" had been completed was less recent than those for whom a "form 2" had not been completed. In the remaining 2 centres, the median date of diagnosis of subjects for whom a "form 2" had been completed was more recent than those for whom a "form 2" had not been completed.

The information retrieved was subsequently inputted and stored on a large database written by this author in Microsoft Access[321], and stored on a stand-alone (unlinked) desk-top computer, which was double password-protected. The database was only constructed 6 months after the commencement of data acquisition; this enabled the database to be constructed with a good concept of the breadth and depth of information which could be retrieved and would be useful for analysis. It was also written after a pilot analysis had been performed on columnar-lined oesophagus segment length, demographic associations and adenocarcinoma risk, which was presented at the annual meeting of the British Society of Gastroenterology in 2003[322].

Data Storage

The Microsoft Access database[321] stored information in a number of linked tables. Patient data which remained constant for each patient, and could have only one value (such as name, date of birth, NHS number) were stored in the central "parent" table, "General Information". Each patient had one record only in the "General Information" table. Other clinical data were stored in 7 linked "child" tables, where each patient could have multiple records, and data values could vary over time (e.g. endoscopy data, weight, medications used). The basic structure of the database is shown in figure 3.F1.

Figure 3.F1 - Basic Structure of the Database

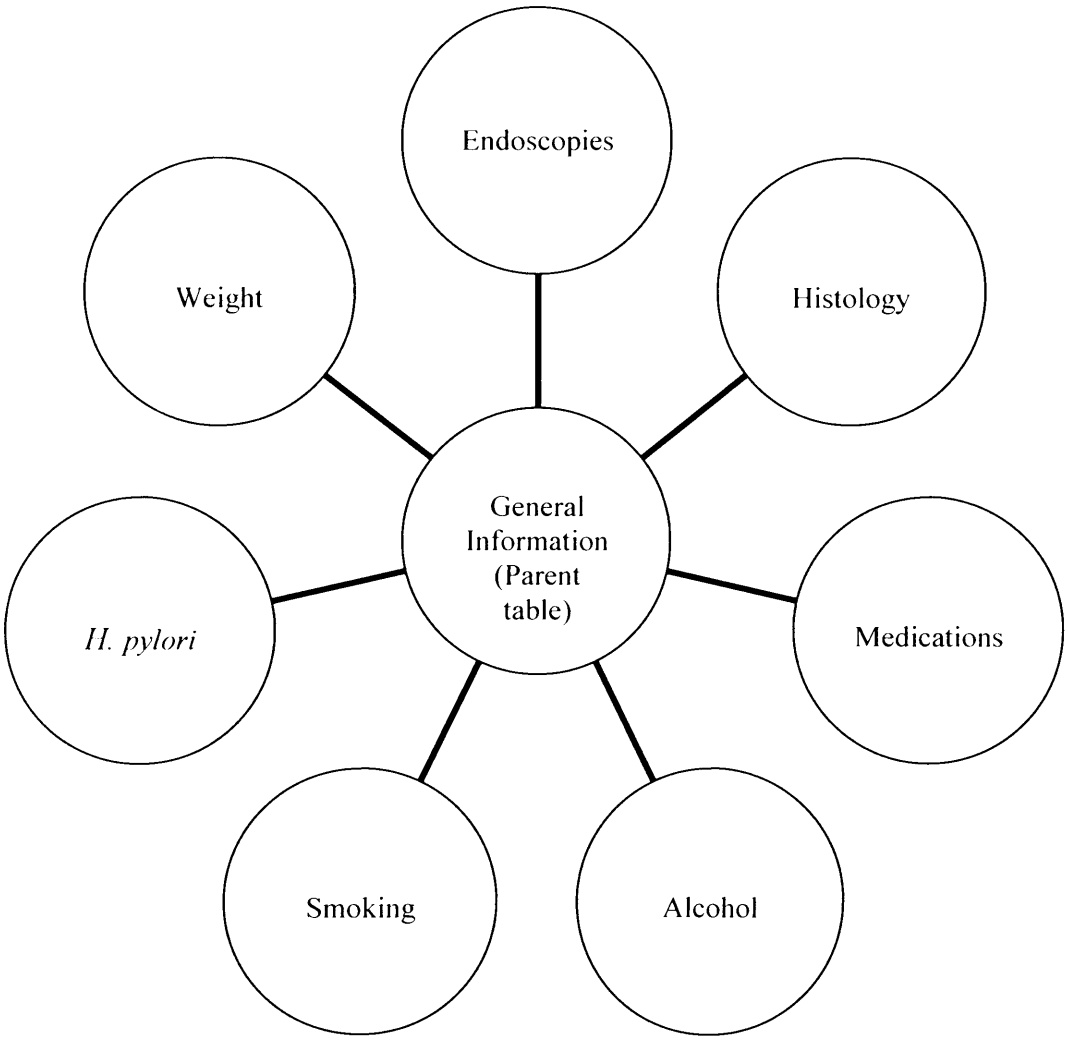


Table 3.T2 describes the basic content of the tables. The full content is described in appendix 4.

Table 3.T2 - Content of Database Tables

Table Name	Parent/Child	Description of Content
General Information	Parent	Name Date of birth Hospital and NHS number Date of Diagnosis of CLO* Date of completion of "form 2" Date and cause of death Date of onset and type of UGI† symptoms Height (to allow calculation of BMI‡) Gastrointestinal comorbidity Genitourinary comorbidity Breast/skin/superficial lesion comorbidity Respiratory comorbidity Cardiovascular comorbidity Haematology comorbidity Orthopaedic and rheumatology comorbidity Neurology and psychiatry comorbidity Date and treatment type for HGD/AC§ Outcome of treatment for HGD/AC§
Endoscopy	Child	Date of endoscopy Indication for endoscopy Position of endoscopic landmarks (and length of CLO* segment) Presence of oesophagitis Presence of oesophageal ulcer Presence of gastritis/gastric ulcer Presence of duodenitis/ duodenal ulcer Presence of oesophageal AC§ and position
Histology	Child	Date of histology Number of biopsies taken Presence of squamous mucosa Presence of columnar mucosa Presence of gastric cardiac mucosa Presence of gastric fundic/body/pyloric mucosa Presence of intestinal metaplasia Presence of changes indefinite for dysplasia Presence of LGD‖ Presence of HGD§ Presence of AC§

Table 3.T2 - Content of Database Tables (continued)

Medications	Child	Date of medications PPI¶ use (type and daily dose) H_2RA¶ use (type and daily dose) Aspirin use NSAID** use Eradication therapy for *H. pylori* All other medications taken
Weight	Child	Date of weight Weight [Kg]
Alcohol	Child	Date of alcohol record Alcohol consumption group††
Smoking	Child	Date of smoking record Smoking habit group††
H. pylori	Child	Date of *H. pylori* record Type of *H. pylori* test Positive/negative test result

* CLO Columnar-lined oesophagus
† UGI Upper gastrointestinal
‡ BMI Body mass index (BMI=weight[Kg]/height[m]^2)
§ HGD High-grade dysplasia, AC adenocarcinoma
|| LGD Low-grade dysplasia
¶ PPI Proton pump inhibitor, H_2RA histamine H_2 receptor antagonist
** NSAID Non-steroidal anti-inflammatory drug
†† For description of alcohol and smoking groups – see appendix 5[229]

These tables were related together using a unique "key" - a code number assigned to each patient, and used to identify and link together the records of each patient between the "parent" and "child" tables. The code also identified which centre had registered the patient, and was called the "UKBOR number". Hence, each patient may have one value only for each variable (and one record only was stored per patient) in the "General Information" (parent) table. Each of the other child tables could contain multiple records for each patient, but the combination of identifying "UKBOR number" and date of record was unique such that a patient could not have two records for the same date, but could have multiple records on multiple occasions.

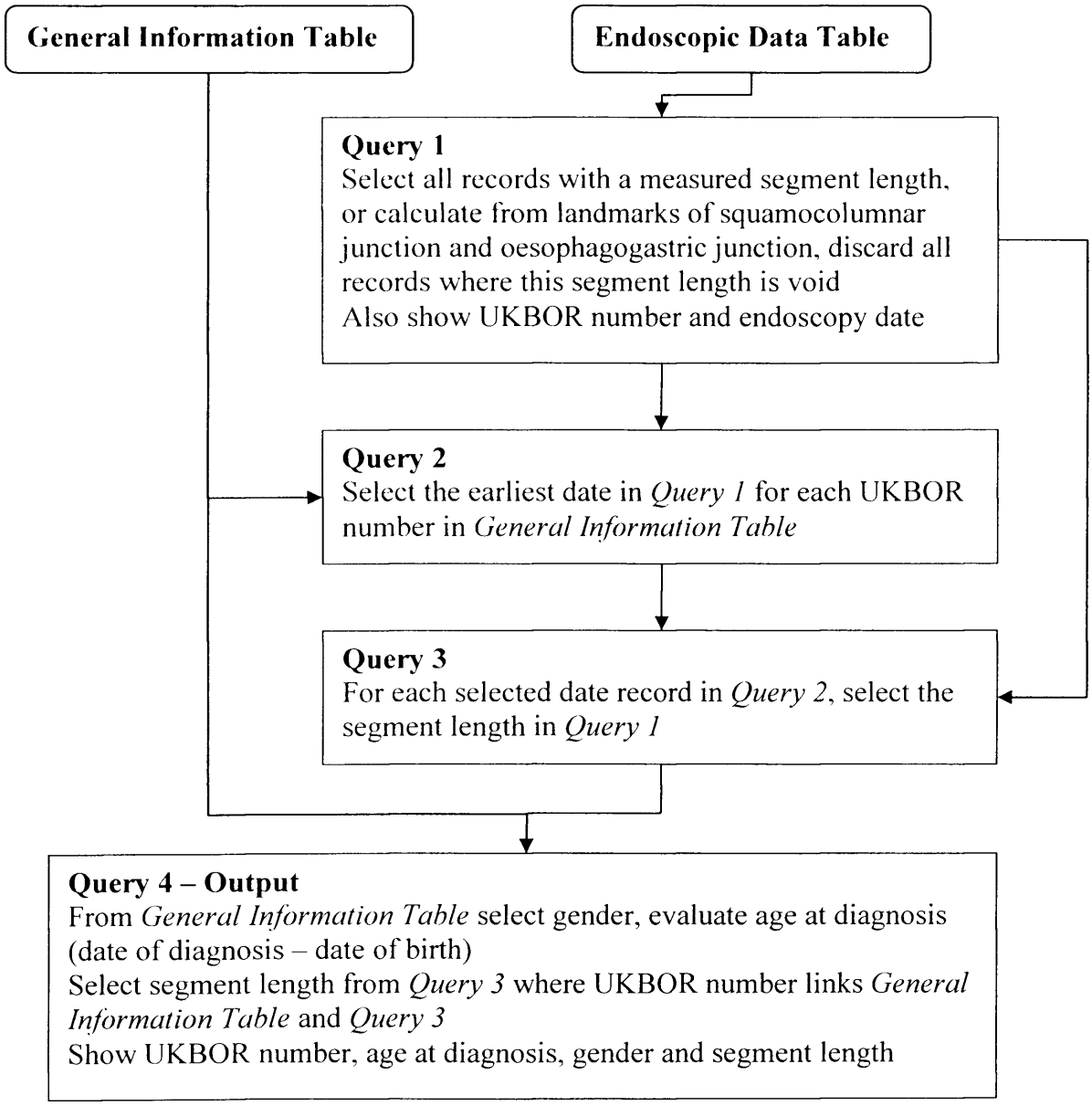
The number of records in each table is shown in table 3.T3:

Table 3.T3 – Number of Records in Each Table

Table Name	Number of Records
General Information	2751
Endoscopy	9513
Histology	4935
Medications	11082
Weight	4384
Alcohol	2204
Smoking	3112
H. pylori	991

In order to extract data from the database, the information in related tables was drawn together and manipulated in order to find the desired data using "select queries" written in the Access query design window and standard query language. Multiple "related queries" were used to select the required records from the tables using criteria specified to determine what characteristics were required for a particular analysis, e.g. the development of dysplasia, endoscopic records including a segment length or patients who had a particular symptom at diagnosis. Queries were also used to perform simple calculations or categorisations, e.g. evaluate the age at diagnosis (from date of diagnosis and date of birth), length of follow-up (from dates of diagnosis and last surveillance), body mass index (from weight and height) and classification of histological reports into the 5 Vienna categories[189]. The structure and capability of queries is very simple, and in order for the required information to be extracted, evaluated and manipulated, several layered queries had to be written, and an example evaluating the age at diagnosis, gender and first segment length measured is shown in figure 3.F2.

Figure 3.F2 – Sample of Structure of Example Query



Data Analyses

Subjects were suitable for analysis in the various results chapters if they fulfilled a number of criteria specified by the queries written to evaluate and retrieve the records specified and perform the calculations required to produce an output table which could be copied into the statistical package for analysis.

Follow-Up of Subjects

The inclusion criteria for patients followed-up over time in the survival analyses are explained in each of the results chapters. As not every patient was biopsied at each endoscopy (especially patients surveyed earlier in the cohort), some patient follow-up has been discarded if the follow-up period is defined as the first to last histology report for each patient.

Some patients who were found to have high-grade dysplasia underwent intervention (oesophagectomy or endoluminal ablation or resection of the columnar mucosa) and the natural history of the columnar-lined oesophagus would be altered by these interventions. Consequently, in many of the analyses, the development of either high-grade dysplasia or adenocarcinoma is defined as the end point. Under these circumstances (where the outcome measure was a histological finding) clearly it is inappropriate to include endoscopies in the follow-up period when biopsies were not taken, and so the follow-up period was defined as the first to last histology report.

Statistical Analysis

The project was overseen by Andre Charlett MSc, head of statistics unit at the Centre for Disease Surveillance and Control, to ensure that the analyses and use of statistics were appropriate.

All statistical analyses were carried out using SPSS[323]. Variables in the analyses could be either continuous (such as height, dates/follow-up time, length of columnarised segment) or categorical (such as gender, presence and grade of dysplasia, whether patients had antireflux surgery).

Analyses of differences between categorical independent and dependent variables (proportional group membership e.g. proportion of males and females [dependent] in each of the centres [independent]) were undertaken using Pearson χ^2. Analyses of differences between continuous dependent variables with categorical independent variables (e.g. age at diagnosis in males and females) were undertaken using unpaired t-test if there were 2 independent categories, or one-way analysis of variance (ANOVA) if there were more than 2 independent categories. As these two tests assume that the data are normally distributed,

and have equal variances. Levene's test of equal variance was used to ensure that these tests were appropriate.

The majority of outcomes in this study are concerned with dysplasia or cancer risk over time. The incidence of oesophageal adenocarcinoma is evaluated by dividing the total number of incident cancers by the total patient-years of follow-up to give a result which was expressed as risk per patient-year. Differences between cancer incidences were examined using Kaplan Meier survival analysis and an exact Poisson model for event occurrence (e.g. development of adenocarcinoma). Subjects were censored (their follow-up was deemed to be terminated) at the time of most recent endoscopy or histopathology report (and the period of follow-up will be defined in the methods section of each of the results chapters). Differences between the rates of event occurrence were examined using Cox proportional hazards ratio, or in the case where there was no hazard in one group (and so a proportional hazards ratio could not be computed), the log-rank test. In the survival analyses, the log minus log plot was also examined to assess for changes in event occurrence between groups, and differences in survival (event occurrence) characteristics were reassessed, ensuring that the curves plotted for the different study groups did not cross. Overall risk differences between subject groups were examined using logistic regression (with follow-up time for each patient as a continuous covariate). Results demonstrating differences between groups in these analyses were expressed as odds ratios. Inter- and intra-observer agreement was evaluated using Cohen kappa statistic[324], where kappa values <0.00 were deemed poor, 0.00-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, 0.81-1.00 near perfect. Evaluated results are expressed as mean average and 95% confidence limits for the mean. p values are given, and values ≤ 0.05 are taken to be significant.

Data Errors

Before analysis, the data were carefully examined for any abnormal values. Dates and values of records were examined to look for any outliers, and these were re-checked against the original "form 2" data. The tables were also examined for any duplicate records (where a subject had more than one record in the table for one date). When duplicate records were found, if any discrepancy existed between them, then the original "form 2" was re-examined, and the discrepancy resolved. The most common occurrence of duplicate

records was in the "Drugs Table". On these occasions there was frequently a discrepancy in the hospital records data which had been transcribed to "form 2", where at one time an incomplete list of medications was recorded, or new medications had been commenced. Under these circumstances, medications were deemed to have been commenced/ceased on the day after they were prescribed/discontinued. If a clear commencement/cessation could not be ascertained from the hospital records, then patients were assumed to be on all medications stated on that date.

Additionally, the validity of the database is discussed further in chapter 9.

Chapter 4 – Epidemiology of the Cohort, Lifestyle Factors and Risk of Adenocarcinoma and High-Grade Dysplasia

Aims and Introduction

Columnar-Lined Oesophagus and Oesophageal Adenocarcinoma

Epidemiological studies have demonstrated a rapid escalation in the incidence of oesophageal adenocarcinoma[4;6;14], overtaking squamous cell carcinoma to become the most common oesophageal malignancy in the UK and USA[5;19-23]. Oesophageal adenocarcinoma is strongly associated with prolonged gastro-oesophageal reflux disease[39] and columnar metaplasia of the oesophageal mucosa[22;29;44-51]. Unfortunately this malignant disease frequently presents late and is incurable at presentation[2;8;69].

Consequently, surveillance is undertaken for patients with columnar-lined oesophagus to enable detection of dysplasia and early adenocarcinoma whilst curative treatment is still possible[91;121]. Surveillance is costly, and so directing practice to those patients at greatest cancer risk, whilst reassuring those at lower risk and lessening the burden of surveillance would be advantageous for both patients and clinicians[122].

Age at Diagnosis

The mean age at diagnosis of columnar-lined oesophagus lies in the 6th and 7th decades of life[36;47;79;84;85;87;88;94;138;168;169;216-224;226]. A large Italian multicentre cohort demonstrates that the highest decade of patient age at diagnosis is 70-79[80]. The columnar-lined oesophagus may already have been present for a considerable time at diagnosis[215] and follow a prolonged period of reflux oesophagitis[224].
The peak decade of diagnosis of adenocarcinoma is older: septuagenarians in both males and females[24-26;29], and the incidence increases with age (and year of birth)[27].

Gender

The male to female ratio in UK-based studies has been reported as 1.6[169] and 1.3[216]. Other studies have reported ratios of 1.3-2.1:1[80;215;217] and even higher rates have been reported by military and veterans' hospitals[36;78;79;224;225]. Compared to patients with reflux oesophagitis, patients with columnar-lined oesophagus are more likely to be male[224]. The male: female ratio is higher in oesophageal adenocarcinoma than columnar metaplasia and has been reported as 3-10:1[4;6;23-25;27-29].

Alcohol Consumption

Alcohol consumption has been varyingly implicated in the epidemiology of columnar-lined oesophagus and as a risk factor for the development of adenocarcinoma. The alcohol consumption of patients with columnar-lined oesophagus has been reported to be the same as that of control populations[78;169;290], patients with reflux oesophagitis[59;229;290] and patients with non-erosive reflux disease[59].

Patients who have been diagnosed with columnar-lined oesophagus who consume alcohol have not been shown to be at greater risk of developing dysplasia than those who do not[222;226]. However, patients with adenocarcinoma have been shown in some series to have a higher alcohol consumption than patients with non-neoplastic columnar-lined oesophagus[228], but the majority of studies have not supported these findings[28;61;223] and one large study has shown the converse: that alcohol drinking overall is associated with a lower risk of adenocarcinoma[24].

Compared to a control population, patients who developed adenocarcinoma of the oesophagus are more likely to consume alcohol (odds ratio 1.6-2.3)[33;34], and a higher alcohol consumption (≥21 units/week) has been shown to be more strongly associated with adenocarcinoma than moderate consumption (odds ratio 2.8)[31].

Smoking Habits

The cigarette smoking habits of patients with columnar-lined oesophagus have been shown to be similar to those of matched controls[78;169;290], and (like alcohol consumption) are similar to those of patients with reflux oesophagitis[59;229;290] and non-erosive reflux disease[59].

Smoking has not been associated either with the development of intestinal metaplasia[76] or dysplasia[222;226] within the columnarised segment. However, smoking is more frequently associated with adenocarcinoma than with columnar-lined oesophagus in some series[28;228], but not others[61;223].

Patients with oesophageal adenocarcinoma were more likely to smoke than a matched control population (odds ratio 2.1-3.4)[31;33-35], with a stronger association for heavier smokers[35], and a weaker (but still significant) association for ex-smokers[35;36].

Obesity

There is no strong association between patients with columnar-lined oesophagus and either weight or body mass index when compared to a control population[78;169] or patients with reflux oesophagitis[229]. However, studies have shown an association between oesophageal adenocarcinoma and obesity[37], which is strongest for patients in the highest quartile[33;37;38] or decile[31] of body mass index when compared to a control population.

Study Cohort

This study uses a subset of patients from centres registering with the UK National Barrett's Oesophagus Registry to examine the epidemiology of columnar-lined oesophagus and progression to adenocarcinoma. This study will attempt to delineate the demographic associations to assist with targeting of surveillance to groups at highest adenocarcinoma risk.

Methods

This analysis was performed on patients who had been diagnosed with columnar-lined oesophagus at 7 centres throughout the UK. The patients were all registered with UKBOR, and were involved in an in-depth analysis on the natural history of columnar-lined oesophagus. Registry researchers visited the centres involved and extracted information from patients' hospital records – typically including endoscopy, histology and operation reports, correspondence following outpatient attendances and inpatient stays. The data were entered into a Microsoft Access database[321]. Patients from the 7 centres were included in the analyses of demographic and lifestyle factors and development of adenocarcinoma if they fulfilled criteria (which were based around the analyses performed).

Patient Selection

Patients were selected if they fulfilled the following criteria:

For general demographic considerations:

1. All patients were included

For analysis of smoking habit, alcohol consumption and obesity:

1. A record of smoking habit/alcohol consumption/weight and height at or preceding diagnosis (to allow calculation of body mass index: weight and height were only recorded if they were dated at least one year prior to diagnosis of columnar-lined oesophagus to prevent bias due from weight loss caused by oesophageal cancer influencing this result)
2. At least one histological biopsy demonstrating columnar-lined oesophagus with or without dysplasia and/or adenocarcinoma

For analysis of prevalent adenocarcinoma frequency (adenocarcinoma detected at or within one year of diagnosis):

1. Only patients who had histological evidence of columnar-lined oesophagus

For analysis of prevalent adenocarcinoma risk with smoking habit, alcohol consumption and obesity:

1. Only patients who had histological evidence of columnar-lined oesophagus
2. For smoking or alcohol risk: a smoking or alcohol score at or preceding diagnosis
3. For obesity risk: a body mass index (BMI calculated as weight[kg]/height[m]^2) as above

For overall adenocarcinoma incidence (adenocarcinoma occurring one year or more from diagnosis of columnar-lined oesophagus):

1. Only patients who had a biopsy demonstrating columnar-lined oesophagus
2. At least one year of follow-up from the date of diagnosis (form 1) to the final endoscopic or histology record (the analysis was performed for both endoscopic and histological follow-up)
    - For endoscopic follow-up, the follow-up period was defined as the period from the first endoscopy demonstrating macroscopic columnar-lined oesophagus to the final endoscopy
    - For histological follow-up, the follow-up period was defined as the period from the first histology report demonstrating columnar-lined oesophagus on biopsy to the final histology report
    - Follow-up was censored at the first histology report demonstrating adenocarcinoma (or high-grade dysplasia when this was the outcome measure) or (if it were earlier) the first endoscopy report demonstrating an oesophageal malignancy which was subsequently corroborated by histopathology
    - If patients underwent oesophagectomy for high-grade dysplasia, then they were censored at the date of the oesophagectomy
3. No prevalent adenocarcinoma
4. For smoking or alcohol risk: a smoking or alcohol score at or preceding diagnosis
5. For obesity risk: a BMI recorded at or prior to the date of columnar-lined oesophagus

Analysis

The demographic breakdown (age and gender) and date of diagnosis of firstly, the entire cohort and secondly, each centre was examined and compared.

The proportion of patients who developed prevalent adenocarcinoma (when diagnosis was considered to be the "diagnosis date" stated on "form 1") was examined and compared between centres.

Comparisons between categorical membership (e.g. gender, presence of prevalent adenocarcinoma) were examined using Pearson's χ^2. Comparison of mean age at diagnosis was examined using ANOVA. The risk of prevalent adenocarcinoma development was examined for smoking habit (with patients grouped into those who had smoked at or within 10 years of diagnosis see appendix 5 [groups 1 and 2 versus 3-5]), alcohol consumption (low and high [groups 1 and 2 versus 3 and 4]) and BMI (examined both as a continuous variable and when subjects were divided into those who were obese [BMI≥30] and non-obese [BMI<30][325]). These analyses were performed using logistic regression with age at diagnosis, year of diagnosis and gender as covariates to allow for their confounding influence.

The overall rates of progression to incident adenocarcinoma and high-grade dysplasia were examined. This analysis was done in three ways:

- Firstly, "endoscopic follow-up for development of adenocarcinoma": the follow-up period was defined as the first endoscopy to the last endoscopy demonstrating columnar-lined oesophagus where subjects were censored at the last endoscopy (with subjects who developed adenocarcinoma or underwent oesophagectomy for high-grade dysplasia censored as above). The outcome measure was development of adenocarcinoma.
- Secondly, "histological follow-up for development of adenocarcinoma": the follow-up period was defined as the first biopsy demonstrating columnar-lined oesophagus to the final oesophageal biopsy. The outcome measure was development of adenocarcinoma.

- Thirdly, "histological follow-up for high-grade dysplasia or adenocarcinoma": the follow-up period was defined as the first biopsy demonstrating columnar-lined oesophagus to the final oesophageal biopsy. The outcome measure was development of adenocarcinoma or high-grade dysplasia.

Analysis of adenocarcinoma development in these three analyses was examined using Kaplan Meier survival analysis and differences between gender, smoking and alcohol groups evaluated using Cox proportional hazards ratio with covariates of gender, age at diagnosis and year of diagnosis. Incidence is modelled using an exact Poisson distribution.

Results

Columnar-Lined Oesophagus: Whole Cohort

Gender and Year of Diagnosis

The proportion of males and females in each centre is shown in table 4.RT1. The overall male to female ratio was 1.67, and there was no significant difference in the proportion of males and females between centres (χ^2=8.525, 6 degrees of freedom, p=0.202). The majority of patients were diagnosed and registered within the last 10 years preceding the termination of data collection (figure 4.RF1). The median date of diagnosis was at the end of 1996. In one centre, the median date of diagnosis occurred after 2000, and in the two largest centres, it lay in 1994 and 1996. The range of date of diagnosis spanned a 29 year period from 1975-2004 (table 4.RT2).

Table 4.RT1 – Gender Breakdown of the Cohort by Registering Centre

Centre*	N Males	N Females	Total
BA	151 (58.5%)	107 (41.5%)	258
HH	53 (59.6%)	36 (40.4%)	89
LP	101 (72.1%)	39 (27.9%)	140
ND	112 (64.0%)	63 (36.0%)	175
RF	180 (61.4%)	113 (38.6%)	293
RY	309 (61.1%)	197 (38.9%)	506
WP	813 (63.0%)	477 (37.0%)	1290
Total	**1719 (62.5%)**	**1032 (37.5%)**	**2751**

* See appendix 3 for centre codes

Figure 4.RF1 – Date of Diagnosis of Subjects

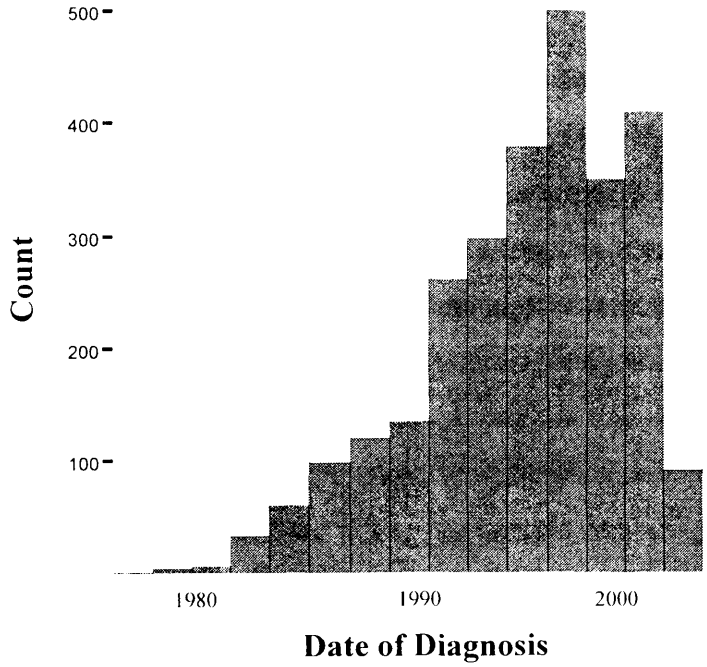


Table 4.RT2 – Date of Diagnosis for Each Centre

Centre	Median	Range
BA	23.05.1998	25.11.1986-17.10.2003
HH	20.04.1998	16.06.1989-08.10.2001
LP	02.04.2000	20.11.1985-11.08.2003
ND	13.11.1996	03.07.1975-26.11.1999
RF	19.10.1995	18.01.1987-02.12.2002
RY	03.12.1994	27.04.1978-09.12.2003
WP	08.12.1996	10.02.1977-02.02.2004
Overall	**13.11.1996**	**03.07.1975-02.02.2004**

Age at Diagnosis

The mean age at diagnosis was 61.1 years in males and 66.7 in females (unpaired 2-tailed t-test $p<0.001$). The median age of males varied from 53.7 to 66.1 between centres, and in females from 64.8 to 71.1. Age at diagnosis varied from pre-teenagers to over 100 years of age.

Prevalent Adenocarcinoma

One hundred and ten patients of 2011 who had histological evidence of columnar-lined oesophagus (5.5%) had prevalent adenocarcinoma. Prevalent adenocarcinoma was more common in males (6.8%) than females (3.1%) (χ^2=12.274, 1 degree of freedom, p<0.001). The proportion of prevalent adenocarcinomata in the individual centres varied between 1.4% and 7.3%, but the numbers were too small to allow meaningful statistical analysis. Seventeen patients had high-grade dysplasia at or within a year of diagnosis of columnar-lined oesophagus. The risk of prevalent adenocarcinoma and high-grade dysplasia combined was higher in males than females (8.1% compared to 3.3% χ^2=18.213, 1 degree of freedom, p<0.001).

Patients who developed prevalent adenocarcinoma were older than those who did not by a mean of 5.4 years, and the odds ratio of 1.04 demonstrates that the risk of prevalent adenocarcinoma increased by 4% for each year increase in age at diagnosis. Prevalent adenocarcinomata were more common in patients diagnosed earlier in the cohort than those diagnosed later, with a reduction in risk of 8% for each year increase that subjects were diagnosed with columnar-lined oesophagus.

The odds ratios for development of prevalent adenocarcinoma dependent on age at diagnosis, gender and year of diagnosis are shown in table 4.RT3.

Table 4.RT3 – Odds Ratio of Prevalent Adenocarcinoma Development

Independent Variable	Odds Ratio	95%CI* for Odds Ratio	P value
Male/Female	2.974	1.833-4.825	<0.001
Age at Diagnosis	1.041	1.024-1.059	<0.001
Year of Diagnosis	0.923	0.892-0.954	<0.001

* CI Confidence Interval

Risk of Smoking Habit, Alcohol Consumption and Obesity on Prevalent Adenocarcinoma

In the whole columnar-lined oesophagus cohort, male patients were more likely to be current or recent smokers (groups 3-5), and have a higher alcohol consumption (groups 3 and 4) than females. Males had a lower mean BMI than females (26.2 versus 26.8) and

there was also a higher proportion of obese females patients (26.7% versus 15.6%). Patients with high alcohol score were more likely to be younger at diagnosis than those with a low alcohol score (mean age 55.8 versus 63.4, independent t-test $p<0.001$). Patients with a high smoking score (3-5) were more likely to be older at diagnosis than those with low smoking score (mean age 55.8 versus 63.4, independent t-test $p<0.001$). There was no difference in the mean age at diagnosis in patients who were obese compared to non-obese patients (t-test non-significant). Consequently, the risk of prevalent adenocarcinoma with smoking, alcohol and body mass index was examined using binomial logistic regression with the outcome measure as adenocarcinoma development within the first year of follow-up. The covariates in the equation were tested individually (as the majority of patients did not have data available on each of these factors): high/low smoking group, high/low alcohol group and BMI (both as a continuous variable and with patients grouped into obese and non-obese). Age at diagnosis, gender and year of diagnosis were also included in the equation to allow for their confounding effects. The analysis was repeated for prevalent high-grade dysplasia and adenocarcinoma grouped together (table 4.RT4). There was no significant risk associated with alcohol consumption group or body mass index (either when examined as a continuous variable, or when patients were grouped as obese/non-obese). High smoking group (smoking at or within 10 years of columnar-lined oesophagus diagnosis) was associated with a higher risk of prevalent adenocarcinoma or high-grade dysplasia.

Table 4.RT4 – Odds Ratio of Prevalent Adenocarcinoma or High Grade Dysplasia/Adenocarcinoma Development with Smoking Habit, Alcohol Consumption and Body Mass Index

Covariate	N Patients	Outcome	N Events	Odds Ratio	95% CI* for Odds Ratio	P value
Alcohol (high/low)	1002	HGD or AC	63	0.571	0.249-1.311	0.186
Alcohol (high/low)	1002	AC	55	0.703	0.303-1.633	0.412
Smoking (high/low)	1147	HGD or AC	79	2.469	1.518-4.018	<0.001
Smoking (high/low)	1147	AC	71	2.410	1.449-4.008	0.001
BMI (continuous)	224	HGD or AC	12	0.944	0.796-1.119	0.504
BMI (continuous)	224	AC	10	0.925	0.780-1.098	0.374
BMI (obese/non-obese)	224	HGD or AC	12	1.005	0.202-4.997	0.995
BMI (obese/non-obese)	224	AC	10	0.531	0.063-4.443	0.559

* CI confidence interval

Overall Adenocarcinoma Incidence

One thousand and three patients had at least one year of endoscopic follow-up. Of these, 28 developed incident adenocarcinoma. The total number of patient-years of follow-up was 5450 (mean 5.43 years, maximum 21.2 years), and median follow-up was 4.47 years. The incidence of adenocarcinoma was 0.0051 cases/patient-year of follow-up (95% confidence intervals for exact Poisson distribution 0.0034 to 0.0074 cases per patient-year), or 1 case in every 195 patient-years of follow-up (95% confidence interval 1 in every 135 patient-years follow-up to 1 in every 293 patient-years follow-up).

Eight hundred and seven patients had at least one year of histological follow-up. Of these, 23 developed incident adenocarcinoma. The total number of patient-years of follow-up was 3912 (mean 4.85 years, maximum 22.9 years), and median follow-up was 4.15 years.

The incidence of adenocarcinoma was 0.0059 (95% confidence interval 0.0038 to 0.0087) cases per patient-year of follow-up, or 1 case in every 170 (95% confidence interval 1 in every 115 to 1 in every 261) patient-years of follow-up.

For incidence of high-grade dysplasia and adenocarcinoma, 806 patients were eligible for analysis. Of these, 39 developed incident high-grade dysplasia or adenocarcinoma. The total number of patient-years of follow-up was 3908 (mean 4.85 years, maximum 22.9 years), and median follow-up was 4.14 years. The incidence of high-grade dysplasia and adenocarcinoma was 0.010 (95% confidence interval 0.0071 to 0.014) cases per patient-year of follow-up, or 1 case in every 100 (95% confidence interval 1 in 73 to 1 in 141) patient-years of follow-up.

Influence of Age and Gender on Adenocarcinoma Incidence

The results for endoscopic follow-up and histological follow-up for differences in adenocarcinoma incidence were similar. Cox proportional hazards ratio demonstrated no statistically significant difference in adenocarcinoma incidence between males and females, or subjects diagnosed earlier or later in the cohort. However, patients who were older at diagnosis were at greater risk of developing incident adenocarcinoma, hazards ratio 1.09 per increase year of age at diagnosis ($p<0.001$)(for both endoscopic and histological follow-up).

For histological follow-up for high-grade dysplasia or adenocarcinoma, there was no significant difference in adenocarcinoma incidence between genders, but the hazards ratio was 1.06 per increase year at age of diagnosis ($p<0.001$).

Smoking, Alcohol and Obesity

Using gender, year of diagnosis and age at diagnosis as covariates, differences between adenocarcinoma incidence were examined using Cox proportional hazards ratio. Unfortunately, less than 200 subjects had a pre-diagnosis BMI, and only 3 of these subjects developed adenocarcinoma and 4 developed high-grade dysplasia. Consequently, survival analyses were not performed on these groups due to the small number of subjects and

events. There was no demonstrable association between alcohol consumption and smoking habit and adenocarcinoma development. The results of the survival analyses are shown in table 4.RT5.

Table 4.RT5 – Cox Proportional Hazards Ratios for Alcohol Consumption, Smoking Habit and Obesity

Covariate	Endoscopic/ Histological Follow-Up	N Patients	Outcome	N Events	Hazards Ratio	95% CI* for Hazards Ratio	P value
Alcohol (high/low)	Endoscopic	570	AC	16	1.733	0.450-6.673	0.424
Alcohol (high/low)	Histological	459	AC	14	1.596	0.326-7.811	0.564
Alcohol (high/low)	Histological	458	HGD or AC	21	1.310	0.363-4.725	0.679
Smoking (high/low)	Endoscopic	662	AC	19	1.277	0.478-3.414	0.625
Smoking (high/low)	Histological	536	AC	17	1.528	0.678-3.442	0.306
Smoking (high/low)	Histological	536	HGD or AC	25	1.893	0.708-5.065	0.204
BMI (continuous)	Endoscopic	198	AC	3	Analysis not done due to small numbers		
BMI (continuous)	Histological	163	AC	2	Analysis not done due to small numbers		
BMI (continuous)	Histological	163	HGD or AC	7	Analysis not done due to small numbers		
BMI (obese/non-obese)	Endoscopic	198	AC	3	Analysis not done due to small numbers		
BMI (obese/non-obese)	Histological	163	AC	2	Analysis not done due to small numbers		
BMI (obese/non-obese)	Histological	163	HGD or AC	7	Analysis not done due to small numbers		

Discussion and Conclusions

The cohort represented in this study is similar in age at diagnosis to others in the UK[85;168;169;216],US[36;47;88;138;215;218;220-222;224;226], France[219], Sweden[87], Switzerland[217;223], Austria[217], Germany[217], The Netherlands[84], Australia[94] and was slightly lower than the multicentric cohort from Italy[80]. The male: female ratio is comparable to another large UK study[169], higher than some European studies[80;216], but lower than others[217], and generally lower than in the US[36;78;79;215;224;225].

The rate of prevalent adenocarcinoma was higher in males than females (actual male: female ratio 3.78:1), which has also been reported by other studies[4;6;23-25;27-29]. The odds ratio for presence of prevalent adenocarcinoma in males compared to females within the cohort was 2.97; however there was no difference in the rates of incident adenocarcinomata or high-grade dysplasia between males and females which does not support any differences in surveillance practice based upon patient gender.

The odds ratio of 0.92 for the year of diagnosis demonstrates that the proportion of prevalent adenocarcinoma (when compared to total number of new diagnoses of columnar-lined oesophagus) was decreasing with time, which is likely to be due to increased use of diagnostic endoscopy and surveillance over time as the number of prevalent adenocarcinomata did not increase or decrease markedly over time from 1990 onwards, despite the increase in number of patients undergoing surveillance as time through the period of the study progressed. The fact that incident adenocarcinoma rate did not vary depending on year of columnar-lined oesophagus diagnosis further supports the observation that this was unlikely to be due to a true fall in adenocarcinoma development in this cohort. The question as to whether the incidence of adenocarcinoma and columnar-lined oesophagus has varied in the populations served by the centres involved in this study cannot be answered without further data on the populations served by the centres. Increases in the prevalence of adenocarcinoma of the oesophagus in the UK have been reported by the West Midlands cancer registry (0.14/100,000 in 1962-66 to 0.76/100,000 in 1982-86)[4] and the Scottish cancer registry(2.2/100,000 to 3.5/100,000 in males and 0.8/100,000 to 1.1/100,000 in females between1976 and 1989)[6]. Increases in the prevalence of columnar-lined oesophagus have also occurred over time (12/6,500 (0.2%)

endoscopies in 1977-81, 267/16,500 (1.6%) endoscopies in 1992-96[73] and 1/100,000 per annum in 1980-81 to 48/100,000 in 1992-93[75]).
Both prevalent and incident adenocarcinoma were more common in patients diagnosed at older ages and the increased association was more apparent with incident than prevalent adenocarcinomata (increased risk of 9% per increased year of age at diagnosis of columnar-lined oesophagus).

Unlike some studies, there was no association in this cohort between alcohol consumption[31;33;34] or body mass index[31;33;37;38] and development (either prevalent or incident) of high-grade dysplasia or adenocarcinoma. The findings of an association with adenocarcinoma development have not been supported by a number of other studies[78;169;290] including studies comparing patients with columnar-lined oesophagus to those with adenocarcinoma[28;61;223] and one study demonstrated an inverse relationship between alcohol consumption and high-grade dysplasia and adenocarcinoma development[24]. The finding of no association between body mass index and adenocarcinoma development may be subject to a type II statistical error, as the number of body mass indexes available was small, but no trend was demonstrated in this cohort.

There was a strong association between smoking and prevalent adenocarcinoma, in keeping with many other studies[31;33-35] including studies on ex-smokers[35;36]. Unlike other studies, we did not demonstrate an association between smoking and incident adenocarcinoma[28;228], but other studies (similarly to this) have also not supported this finding[61;223] and this issue remains controversial.

The overall adenocarcinoma incidence was 1/195 patient-years of follow-up when follow-up was defined as the first to last endoscopy for columnar-lined oesophagus. This is likely to be an underestimate of the true adenocarcinoma incidence due to failure to biopsy (preventing discovery of early adenocarcinomata - which are invisible to the standard examining endoscope). Similarly, taking the histological incidence of 1/170 may underestimate the true adenocarcinoma incidence as it is biased by patients with lesions visible to the endoscope being more likely to be biopsied, and macroscopic mucosal lesions have been shown to be associated with progression to adenocarcinoma[97]. Both of these estimates of adenocarcinoma incidence are subject to biases in surveillance practice at the

registering centres, and patients with high-grade dysplasia undergoing intervention (oesophagectomy or endoluminal therapy) and consequently altering the natural history of the segment. These biases are overcome to some degree by examining the rate of progression to high-grade dysplasia (1/100 patient-years follow-up), but the finding of high-grade dysplasia or microscopic adenocarcinoma is subject to sampling error[275] and variations in histopathological diagnosis[189,280-282].

Appendix 1 shows the annual incidence of adenocarcinoma from a literature search which yielded 40 studies stating adenocarcinoma incidence in patients with columnar-lined oesophagus. The overall annual incidence was 0.69% (95% confidence interval 0.60-0.79%); this is similar to the results of this study for endoscopic follow-up (0.51% per annum, 95% confidence interval 0.34-0.74) and histological follow-up (0.59% per annum, 95% confidence interval 0.38-0.87).

In conclusion, this study did not demonstrate an association between gender, smoking habits, alcohol consumption or body mass index and incident adenocarcinoma development, and does not support basing surveillance programmes for adenocarcinoma on any of these factors. Although prevalent adenocarcinomata were more frequent in males, older patients and those who smoked, only age at diagnosis correlated with an increased risk of incident carcinoma. During the period studied, the rate of incident adenocarcinomata did not increase with year of columnar-lined oesophagus diagnosis, but a population-based study would be required to resolve this point.

Chapter 5 - Changes in the Columnar Segment Over Time

Aims and Introduction

Columnar-Lined Oesophagus and Oesophageal Adenocarcinoma

The association between gastro-oesophageal reflux disease and development of columnar metaplasia of the lower oesophagus is well established[81;149-151]. Patients who develop columnar metaplasia of the oesophagus have been shown to have more defective anti-reflux mechanisms over patients with simple reflux oesophagitis[60] and consequently higher oesophageal exposure to refluxing acid[61;63] and bile[62;63]. The combination of both acidic gastro-oesophageal reflux and reflux of small intestinal contents into the oesophagus is more closely associated with the development of columnar metaplasia than either alone[64;65]. The association between columnar-lined oesophagus and neoplastic change in this metaplastic epithelium has been reported for over 40 years[42-44], and patients with columnar metaplasia are estimated to have 5-125x the risk of developing oesophageal adenocarcinoma when compared to a control population[86;89;92;168;169], but the clinical prevalence of columnar-lined oesophagus represents only a small fraction of the total prevalence as determined by autopsy studies on the general population[72]. Consequently, the American College of Gastroenterology[91] recommends surveillance and the British Society of Gastroenterology[121] recommends consideration of surveillance of patients who are known to have columnar-lined oesophagus to detect dysplasia and early adenocarcinoma to allow intervention before the tumour becomes incurable[2;8;69;91;100-105].

Surveillance of patients with columnar-lined oesophagus is costly, both in terms of clinical resources[117-120] and models do not take into account time taken off from work to attend the hospital or psychological cost of screening and surveillance. Additionally, surveillance has never been shown to improve overall survival[86;89;122;221], but surveillance-detected adenocarcinomata present at earlier stage[100-105] and have improved survival over adenocarcinomata presenting clinically[100;101;103-105]. Furthermore, the risk of adenocarcinoma development is no higher than in patients with Schatzki ring or achalasia[230] and only a small fraction of patients with columnar-lined oesophagus progress to develop adenocarcinoma. The majority (more than 95%) of patients with columnar-lined

oesophagus die of unrelated causes[86;221;230]. Consequently, programmes of targeted surveillance[122] following those patients at highest risk of adenocarcinoma development are more attractive to reduce the clinical and financial burden of current surveillance practice and could reduce patients' psychological distress.

Association Between Metaplastic Segment Length and Adenocarcinoma Risk

Both dysplasia and adenocarcinoma may occur in shorter[196;253] and longer[87-89;251;258] segments of columnar-lined oesophagus. The magnitude of oesophageal acid and bile exposure and frequency of symptoms are higher in patients with long (≥3cm) segment than short segment columnar-lined oesophagus[66] and this increased severity of oesophageal exposure to these injurious components of reflux would logically be associated with a higher cancer risk. Clinical studies have supported this theory with a higher risk of dysplasia[251;258] and adenocarcinoma[87-89] demonstrated in patients with long (≥3cm) segments of columnar-lined oesophagus. Additionally, a case-control study found that the segment length in patients with high-grade dysplasia or adenocarcinoma was higher than in those with non-dysplastic columnar-lined oesophagus[61]. In 1997, 27% of UK clinicians who performed surveillance for columnar-lined oesophagus based their decision to perform surveillance (at least in part) on the length of metaplastic segment[244]; and in 2001, 69% of UK clinicians performing columnar-lined oesophagus surveillance were only including patients with ≥3cm segments in their surveillance programmes[245]. The current US[91] and UK guidelines[121] state that the decision to perform surveillance should not be based on metaplastic segment length.

One study has previously examined adenocarcinoma risk stratified by metaplastic segment length. Rudolph *et al.*[90] demonstrated a trend for higher cancer risk in longer metaplastic segments of 309 patients, but this trend did not reach statistical significance.

Changes in Metaplastic Segment Length Over Time

Multiple studies have demonstrated small increases[168;259;260] and decreases[134;153;198;219;259-268] in the length of the metaplastic segment over time. Development of isolated islands of squamous re-epithelialisation have also been demonstrated[153;261;269]. However, neither acid suppression medication nor antireflux surgery results in a reliable reduction in the length of the metaplastic segment. Overall, the segment length involved develops early (Cameron *et al.*[215] suggest approximately 20 years on average prior to diagnosis) and does not change with time[199;215;270].

If the adenocarcinoma risk is dependent upon metaplastic segment length, then in order to stratify patient risk on this basis, it must be possible to measure segment length accurately and consistently. A number of studies have demonstrated significant inter- and intra-observer variability both in models of oesophageal columnar metaplasia[200] and in-vivo studies[197-199]. Sixty percent of the time observers tended to consistently over- or underestimate the true length[200].

Association Between Histology and Adenocarcinoma Risk

The US American College of Gastroenterology guidelines[91] recommend surveillance of all visible columnar metaplasia which demonstrates intestinal metaplasia on biopsy, as this is the metaplastic tissue type most frequently found in association with oesophageal adenocarcinoma[29;44-46;48-50;87;182-187;252]. Intestinal metaplasia and dysplasia do not have any distinguishing features from cardiac or fundic metaplasia of the oesophagus when viewed with a standard endoscope. These are examined for on histological examination of biopsy specimens. Whilst the importance of intestinal metaplasia in the sequence of events leading to adenocarcinoma is well-accepted, the events leading to intestinal metaplasia are less well understood. The finding of goblet cells (signifying intestinal metaplasia[179]) is subject to significant sampling error[197;252-255] and studies have demonstrated that the prevalence of finding intestinal metaplasia increases with patient age[247;248], cumulatively with number of surveillance endoscopies[249], experience of the endoscopist[254], number of biopsies taken from the metaplastic segment[256], increased length of gastro-oesophageal reflux symptoms[250], increased oesophageal exposure to bile[250] and macroscopic length of columnarised segment[249;251] - which (with the exception of the number of surveillance

endoscopies, biopsies taken and experience of the endoscopist) have each been associated with higher adenocarcinoma risk[27,39,87-89].

Additionally, patients who were first diagnosed with columnar-lined oesophagus without intestinal metaplasia have subsequently demonstrated intestinal metaplasia on further surveillance biopsies and later progressed to adenocarcinoma[87], and studies have suggested a progression from squamous mucosa to intestinal metaplasia involving cardiac metaplasia[186,252]. Oesophageal biopsy samples without clear evidence of goblet cells have also been shown to be positive for immunohistochemical markers for intestinal differentiation[257]. Pathological opinion in the UK believes that if sufficient biopsies are taken over an adequate time period then intestinal metaplasia will always be found in the columnar-lined oesophagus[188]. As a consequence, the British Society of Gastroenterology guidelines recommend that the decision to enrol a patient into surveillance should not be based on the presence or absence of intestinal metaplasia[121,256] and in 1997 only 12% of UK clinicians undertaking surveillance based this on the presence or absence of intestinal metaplasia[244].

Dysplasia is the best current indicator of risk of cancer and is the basis on which the surveillance interval is determined[91], with shorter intervals recommended for higher grades of dysplasia. The confirmed finding of high-grade dysplasia is considered by many clinicians to be grounds for oesophagectomy or endoluminal therapy because of the likelihood of the development of invasive adenocarcinoma[244-246]. Three studies have reported adenocarcinoma only developing in patients who had previously demonstrated dysplasia[92-94]. Dysplasia (when it develops) is also not homogenously dispersed throughout the whole segment. Cameron *et al.*[273] reported that in resection specimens for high-grade dysplasia or early adenocarcinoma, the median area of columnar-lined oesophagus was 32cm^2, low-grade dysplasia 13cm^2, high-grade dysplasia 1.3cm^2 and adenocarcinoma 1.1cm^2. They also demonstrated multifocal non-confluent areas of dysplasia and carcinoma, which could be missed by multiple systematic biopsies[275]. An analysis of 15 studies examining the frequency of occult adenocarcinoma in oesophagectomy specimens following a pre-operative diagnosis of high-grade dysplasia found this to be 43% overall[96]. Other studies have indicated that the probability of occult adenocarcinoma increases with more extensive high-grade dysplasia[97,276] and the presence of any mucosal lesion[97].

The risk of adenocarcinoma in columnar-lined oesophagus overall is 0.69% per annum see appendix 1. Two studies have reported adenocarcinoma risk in low-grade dysplasia. Skacel *et al.*[95] demonstrated that 7 of 25 patients with a diagnosis of low-grade dysplasia developed high-grade dysplasia or adenocarcinoma at a mean follow-up of 26 months (annual incidence 12.9%), and the risk was higher in patients where there was a higher level of agreement between histopathologists.

Reid *et al.*[47] reported that 3 of 43 patients with low-grade dysplasia developed adenocarcinoma (annual incidence 12%). All of the patients who developed adenocarcinoma had aneuploidy, or an increased 4N fraction on flow cytometry. The risk of adenocarcinoma developing when high-grade dysplasia is present is higher. Schnell *et al.*[277] followed-up 79 patients with high-grade dysplasia for 7.3 years, during which time the adenocarcinoma incidence was 2.2% in the first year and 2.1% per annum overall. All of the adenocarcinomata which developed were detected at a curable stage (with the exception of one in a patient who had defaulted follow-up). They concluded that their 3 monthly surveillance protocol caught adenocarcinoma at a curable stage, and did not recommend oesophagectomy for high-grade dysplasia alone. Buttar *et al.*[97] found that overall 27.8% of patients in their cohort of 100 patients with high-grade dysplasia developed adenocarcinoma in the first year, and that the annual adenocarcinoma incidence over the first 3 years was 14.0%. Romagnoli *et al.*[278] looked at patients with high-grade dysplasia and compared patients operated on immediately after the diagnosis to those whose high-grade dysplasia persisted or progressed to adenocarcinoma at 6 months (and underwent oesophagectomy at that point) to the third group of patients who underwent oesophagectomy when they developed symptoms of dysphagia or biopsies demonstrated adenocarcinoma after 6 months. They demonstrated that the cancer-related survival was 100% in those operated-on immediately, but only 52.5% in those surveyed for 6 months or more, and advised oesophagectomy as the treatment of choice in high-grade dysplasia. Rudolph *et al.*[90] showed that the annual incidence of adenocarcinoma in patients with high-grade dysplasia was 23.0%, compared to 0.8% in patients without high-grade dysplasia at diagnosis.

Studies of Interobserver Agreement in Grading of Dysplasia

The gold standard for grading of dysplasia in columnar-lined oesophagus is histological interpretation of biopsy specimens. The interobserver variability in comparing high-grade dysplasia and adenocarcinoma to columnar-lined oesophagus with no dysplasia, changes indefinite for dysplasia and low-grade dysplasia is low: 85% and 87% agreement on successive reviews of slides by Reid *et al.* in 1988[280] and kappa values 0.66 before and 0.70 after a consensus meeting reported by Montgomery *et al.* in 2001[281]. This distinction into two groups determines which patients need immediate re-biopsy or further investigations with consideration of surgical resection, but does not help to determine an appropriate follow-up interval in the majority of patients who do not have high-grade dysplasia or adenocarcinoma. When divided into all of the Vienna categories[189], the interobserver variability before the consensus meeting was 14% (kappa 0.01), and after the consensus meeting was 63% (kappa 0.31)[189]. Interobserver agreement grading non-dysplastic columnar-lined oesophagus, changes indefinite for dysplasia, low-grade dysplasia, and the fourth group of high-grade dysplasia and adenocarcinoma was moderate both pre- and post the consensus meeting (kappa=0.43 pre- and post-meeting)[281]. Overall, interobserver agreement is least variable at both ends of the histological spectrum of dysplasia[189;281]. The interobserver agreement between 3 pathologists for the diagnosis of low-grade dysplasia was poor (kappa 0.17, actual agreement 45.7%)[95]. Recently, Ormsby *et al.*[282] examined interobserver agreement between 2 gastrointestinal pathologists and one general pathologist on the diagnoses of high-grade dysplasia, intramucosal adenocarcinoma and invasive adenocarcinoma. They found that the overall agreement for these diagnoses was fair (kappa=0.59), and between the gastrointestinal pathologists agreement was good (kappa=0.68). Comparing high-grade dysplasia to intramucosal adenocarcinoma, the agreement between all pathologists was fair (kappa=0.42) and between gastrointestinal pathologists was also fair (kappa=0.56). Comparing high-grade dysplasia to submucosal adenocarcinoma (the stage at which tumour spread to involve lymph nodes occurs much more frequently[71] necessitating a more radical approach to resection than treatment of the mucosa only), agreement was perfect (kappa=1.00) between all pathologists, and comparing intramucosal adenocarcinoma to submucosal carcinoma: agreement was good between all pathologists (kappa=0.71) and gastrointestinal pathologists (kappa=0.76).

The analyses in this chapter examine for differences in adenocarcinoma risk (both prevalent and incident) when patients are grouped by metaplastic segment length and also differences in incident adenocarcinoma (and high-grade dysplasia) risk dependent on diagnostic histology to examine for those patients who might benefit most from surveillance.

Methods

This analysis was performed on patients who had been diagnosed with columnar-lined oesophagus at 7 centres throughout the UK (see appendix 3). The patients were all registered with UKBOR, and were involved in an in-depth analysis on the natural history of columnar-lined oesophagus. Registry researchers visited the centres involved and extracted information from patients' hospital records – including endoscopy, histology and operation reports, correspondence following outpatient attendances and inpatient stays. The data were entered into a Microsoft Access database[321]. Patients from the 7 centres were included in the analyses of changes in segment length, interobserver variability in length measurement, progression or regression of columnarised segment length and differences in adenocarcinoma risk dependent on segment length and histology if they fulfilled criteria, which were based around the analyses performed.

Patient Selection

Patients were selected if they fulfilled the following criteria:

For analysis of prevalent adenocarcinoma incidence dependent on segment length:

1. Only patients who had histological evidence of columnar-lined oesophagus and adenocarcinoma demonstrated histologically (or endoscopically and confirmed histologically) within one year of diagnosis of columnar-lined oesophagus
2. Patients who had a segment length recorded at or following diagnosis of columnar-lined oesophagus

For analysis of adenocarcinoma incidence dependent on segment length and diagnostic histology:

1. Only patients who had a biopsy demonstrating columnar-lined oesophagus. The first biopsy demonstrating columnar-lined oesophagus was taken to be the diagnostic histology
2. At least one year of follow-up from the date of histological diagnosis to the final histology record

3. The follow-up period was defined as the period from the first histology report demonstrating columnar-lined oesophagus to the final histology report
4. Follow-up was censored at the first histology report demonstrating adenocarcinoma (or high-grade dysplasia when this was the outcome measure) or (if it were earlier) the first endoscopy report demonstrating an oesophageal malignancy which was subsequently corroborated by histopathology
5. If patients underwent oesophagectomy for high-grade dysplasia, then they were censored at the date of the oesophagectomy
6. No prevalent adenocarcinoma
7. For analysis of incident adenocarcinoma risk and segment length: patients who had segment length recorded at or following diagnosis of columnar-lined oesophagus

For analysis of interobserver agreement in segment length groups at first and second segment length measurements:

1. Only patients who had a biopsy demonstrating columnar-lined oesophagus
2. At least two segment lengths measured on separate occasions

For analysis of variability of segment length measurement from diagnostic and mean length:

1. Only patients who had a biopsy demonstrating columnar-lined oesophagus
2. At least 3 segment length measurements

For overall analysis of changes in segment length from diagnostic length grouped by the most dysplastic histology attained:

1. Only patients who had a biopsy demonstrating columnar-lined oesophagus
2. At least two segment lengths measured on separate occasions

For progression/regression of segment length over time:

1. Only patients who had a biopsy demonstrating columnar-lined oesophagus
2. At least 3 segment length measurements
3. Segment length measurements made in the two five year bands following diagnosis

The date of diagnosis was considered to be the first histological confirmation of columnar-lined oesophagus.

For analysis of segment length: patients were separated into 4 groups, similarly to Rudolph *et al.*[90] (table 5.MT1). Patients were not included in the analysis if the endoscopy record stated only the presence of a "short segment" or "long segment" of columnar-lined oesophagus due to difficulties in reliably classifying these patients and different interpretations of what constituted "long" and "short" segments of columnar metaplasia[91;122;192;201;202]. For interobserver variation in segment length and validation of the use of the first segment length to determine segment length group, the first two segment lengths were classified into the groups in the segment length table (table 5.MT1) and interobserver agreement examined using kappa statistics[324].

Table 5.MT1 – Segment Length Groups

Segment Length
≤3cm
>3 ≤6cm
>6 ≤9cm
>9cm

For analysis of adenocarcinoma risk dependent on diagnostic histology, patients were grouped into the 5 Vienna classification categories[189], with the addition of a further group, separating non-dysplastic columnar-lined oesophagus into patients without evidence of intestinal metaplasia and those with intestinal metaplasia (table 5.MT2).

Table 5.MT2 – Histology Groups

Histology Group	Description
CLO-	Columnar-lined oesophagus without intestinal metaplasia or dysplasia
CLOIM	Columnar-lined oesophagus with intestinal metaplasia and without dysplasia
Indefinite for dysplasia	Columnar-lined oesophagus with changes indefinite for dysplasia
LGD	Columnar-lined oesophagus with low-grade dysplasia
HGD	Columnar-lined oesophagus with high-grade dysplasia
AC	Adenocarcinoma

Comparisons between categorical membership (e.g. segment length group, presence of prevalent adenocarcinoma) were examined using Pearson's χ^2. Comparison of mean age at diagnosis was examined using ANOVA. The risk of prevalent adenocarcinoma development was examined for segment length and diagnostic histology. These analyses were performed using logistic regression with age at diagnosis, year of diagnosis and gender as covariates to allow for their confounding influence.

The overall rates of progression to incident adenocarcinoma and high-grade dysplasia were examined. This analysis was done in 2 ways as many patients have the natural history of their metaplastic segment altered by interventions when high-grade dysplasia had been detected:

- Firstly, "histological follow-up for development of adenocarcinoma": the follow-up period was defined as the first biopsy demonstrating columnar-lined oesophagus to the final oesophageal biopsy. The outcome measure was development of adenocarcinoma.
- Secondly, "histological follow-up for high-grade dysplasia or adenocarcinoma": the follow-up period was defined as the first biopsy demonstrating columnar-lined oesophagus to the final oesophageal biopsy. The outcome measure was development of adenocarcinoma or high-grade dysplasia.

Adenocarcinoma development in these 2 analyses was examined using Kaplan-Meier survival analysis and differences between segment length groups and diagnostic histology groups evaluated using Cox proportional hazards ratio with covariates of gender, age at

diagnosis and year of diagnosis. Patients were only included in incidence analyses if their follow-up period was at least 1 year, and data was modelled using an exact Poisson distribution.

Variability in segment length measurement was examined by looking at changes from each patients most outlying segment length to diagnostic segment length and from most outlying segment length to average segment length.

Changes in measured segment length over time were examined in two ways. Firstly, the change from the diagnostic length to the mean length in the first 5 years of follow-up, mean length in the second 5 years of follow-up, and third and fourth five year bands of follow-up were examined using analysis of variance. Secondly, overall progression and regression of segment length was examined looking for patients whose segment length either consistently increased or decreased from the diagnostic length to the mean length in the first 5 years of follow-up to the second 5 years of follow-up. These analyses for change in segment length were performed for patients grouped into 3 groups dependent on the most dysplastic histology attained: 1) no dysplasia, 2) low-grade dysplasia and 3) high-grade dysplasia/adenocarcinoma.

Results

One thousand eight hundred and thirty two patients had histological evidence of columnar-lined oesophagus, and were included in the cohort. Of these, 1349 had one segment length measurement and were appropriate for the segment length analysis. The kappa coefficient for interobserver variability between the 763 patients who had at least 2 segment lengths measured (grouped as in table 5.MT1) was 0.37 (fair agreement). Averaging all patients' segment lengths over time, there was no significant change in segment length over time when the cohort was examined as a whole. This is presented in detail at the end of the results section (figures 5.RF5 and 5.RF6).

Prevalent Adenocarcinoma and High-Grade Dysplasia

Thirty seven (2.7%) of the 1349 patients with a measured segment length were deemed to have prevalent adenocarcinoma. Prevalent adenocarcinoma did not occur equally in all groups, but was higher in the longer segment (>6 ≤9cm and >9cm) groups (overall Pearson χ^2 3 degrees of freedom p=0.029). Combining prevalent high-grade dysplasia and adenocarcinoma (50 patients, 3.7% of cohort) also demonstrated that these two diagnoses occurred more frequently in the longer segment groups (overall Pearson χ^2 3 degrees of freedom p=0.009). The results are shown in table 5.RT1.

Table 5.RT1 – Distribution of Prevalent Adenocarcinoma and High-Grade Dysplasia by Segment Length Group

Length Group	N in Length Group(%*)	N (%†) Prevalent Adenocarcinoma	N (%†) Prevalent High-Grade Dysplasia/Adenocarcinoma
≤3cm	443 (32.8%)	10 (2.3%)	12 (2.7%)
>3 ≤6cm	496 (36.8%)	9 (1.8%)	12 (2.4%)
>6 ≤9cm	210 (15.6%)	12 (5.7%)	13 (6.2%)
>9cm	200 (14.8%)	6 (3.0%)	13 (6.5%)

* Percent of total cohort
† Percent of segment length group

Patients with longer segments of columnar-lined oesophagus were on average older at diagnosis of columnar-lined oesophagus than those with shorter segments (ANOVA

$p<0.001$), but there was no difference in the gender distribution (χ^2 3 degrees of freedom $p=0.125$) or year of diagnosis (ANOVA $p=0.315$) between the segment length groups (Table 5.RT2).

Table 5.RT2 – Age and Gender Breakdown by Segment Length Group

Length Group	Median Age at Diagnosis	N (%) Males	N (%) Females
≤3cm	60.2	273 (61.6%)	170 (38.4%)
>3 ≤6cm	61.2	340 (68.5%)	156 (31.5%)
>6 ≤9cm	65.2	138 (65.7%)	72 (34.3%)
>9cm	67.0	137 (68.5%)	63 (31.5%)
Total	62.2	888 (65.8%)	461 (34.2%)

To allow for the potential confounding factors of age at diagnosis, gender and year of diagnosis, binary logistic regression was performed entering them as covariates for development of prevalent adenocarcinoma (table 5.RT3) or prevalent high-grade dysplasia and adenocarcinoma (table 5.RT4). When gender, age at diagnosis and year of diagnosis were entered as covariates into the binary logistic regression, there was still a trend for prevalent adenocarcinoma and high-grade dysplasia to occur more frequently in the longer segments (>6 ≤9cm and >9cm groups). This did not reach statistical significance for either adenocarcinoma or high-grade dysplasia and adenocarcinoma together; and there was no overall risk in development of prevalent adenocarcinoma or prevalent high-grade dysplasia or adenocarcinoma comparing short (≤3cm) to long (>3cm) columnar-lined oesophagus.

Table 5.RT3 – Logistic Regression of Development of Prevalent Adenocarcinoma

Factor	P value	Odds Ratio	95% CI* for Odds Ratio
Gender (M/F)	0.100	1.916	0.883-4.158
Age at Diagnosis	0.030	1.032	1.003-1.061
Year of Diagnosis	0.562	0.980	0.917-1.048
Segment >3 ≤6cm†	0.537	0.750	0.301-1.870
Segment >6 ≤9cm†	0.059	2.302	0.969-5.466
Segment >9cm†	0.894	1.074	0.379-3.045
All Long Segment†	0.666	1.177	0.561-2.472

* CI Confidence Interval

† Compared to short segment (≤3cm) columnar-lined oesophagus

Table 5.RT4 – Logistic Regression of Development of Prevalent High-Grade Dysplasia or Adenocarcinoma

Factor	P Value	Odds Ratio	95% CI* for Odds Ratio
Gender (M/F)	0.014	2.460	1.201-5.038
Age at Diagnosis	0.004	1.037	1.011-1.062
Year of Diagnosis	0.716	1.011	0.952-1.075
Segment >3 ≤6cm†	0.664	0.835	0.369-1.887
Segment >6 ≤9cm†	0.081	2.059	0.914-4.641
Segment >9cm†	0.111	1.947	0.857-4.422
All Long Segment†	0.351	1.374	0.705-2.676

* CI Confidence Interval

† Compared to short segment (≤3cm) columnar-lined oesophagus

Analysis of Incident Adenocarcinoma and High-Grade Dysplasia Development

Seven hundred and eight patients were eligible for analysis of adenocarcinoma incidence dependent on segment length group. The overall mean follow-up was 5.05 years, total 3575 patient-years follow-up. Of these, 22 developed incident adenocarcinoma, and 36 developed incident high-grade dysplasia or adenocarcinoma.

Patients with longer segments of columnar-lined oesophagus were older at diagnosis than those with shorter segments (table 5.RT5). There was no significant difference in the gender distribution or in the year of columnar-lined oesophagus diagnosis between the segment length groups. There was no association between gender or age at diagnosis and diagnostic histology group.

Table 5.RT5 – Age at Columnar-Lined Oesophagus Diagnosis and Segment Length Group

Segment Length Group	Median Age at Diagnosis
≤3cm	57.8
>3 ≤6cm	59.4
>6 ≤9cm	63.8
>9cm	65.5

ANOVA $p<0.001$ for comparison of mean age at diagnosis

Patients with longer segments of columnar-lined oesophagus were also more likely to have intestinal metaplasia and dysplasia at diagnostic biopsy, with one third of patients with segments ≤6cm not having intestinal metaplasia at columnar-lined oesophagus diagnosis, and only 7% having dysplasia, whereas in segment length groups >6cm only 19.6% did not have intestinal metaplasia on diagnostic biopsy, and 12.8% had dysplasia. The diagnostic histology and segment length breakdown of the cohort is shown in table 5.RT6.

Table 5.RT6 – Diagnostic Histology and Segment Length Breakdown of Cohort

Segment Length Group	CLO-† N (%)*	CLOIM† N (%)*	Indefinite for Dysplasia N (%)*	Dysplasia N (%)*	Total N (%)‡
≤3cm	66 (31.9%)	110 (53.1%)	18 (8.7%)	13 (6.3%)	207 (29.2%)
>3 ≤6cm	96 (34.0%)	149 (52.8%)	16 (5.7%)	21 (7.4%)	282 (39.8%)
>6 ≤9cm	26 (22.4%)	68 (58.6%)	11 (9.5%)	11 (9.5%)	116 (16.4%)
>9cm	17 (16.5%)	55 (53.4%)	14 (13.6%)	17 (16.5%)	103 (14.5%)
Total	205 (29.0%)	382 (54.0%)	59 (8.3%)	62 (8.8%)	708 (100%)

Overall Pearson χ^2 12 degrees of freedom p=0.007
* Percentage of Segment Length Group
† CLO- Columnar-Lined Oesophagus Without Intestinal Metaplasia
† CLOIM Columnar-lined oesophagus With Intestinal Metaplasia
‡ Percentage of Whole Cohort

The Kaplan-Meier survival plots for demonstration of incidence adenocarcinoma and both high-grade dysplasia and adenocarcinoma together dependent on segment length group are shown in figures 5.RF1 and 5.RF2. Figures 5.RF3 and 5.RF4 show the Kaplan-Meier plots for development of incident adenocarcinoma and both high-grade dysplasia and adenocarcinoma together dependent on diagnostic histology group.

Figure 5.RF1 – Kaplan Meier Survival Plot for Development of Incident Adenocarcinoma Dependent on Segment Length Group

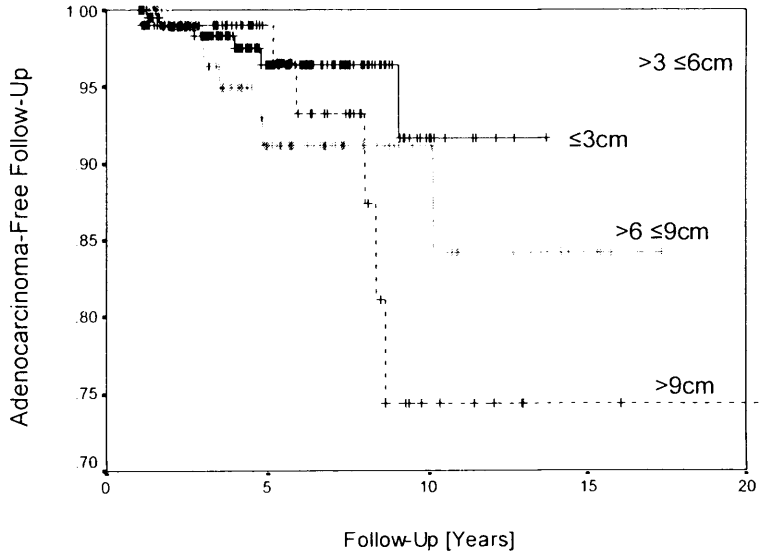


Figure 5.RF2 – Kaplan Meier Survival Plot for Development of Incident High-Grade Dysplasia or Adenocarcinoma Dependent on Segment Length Group

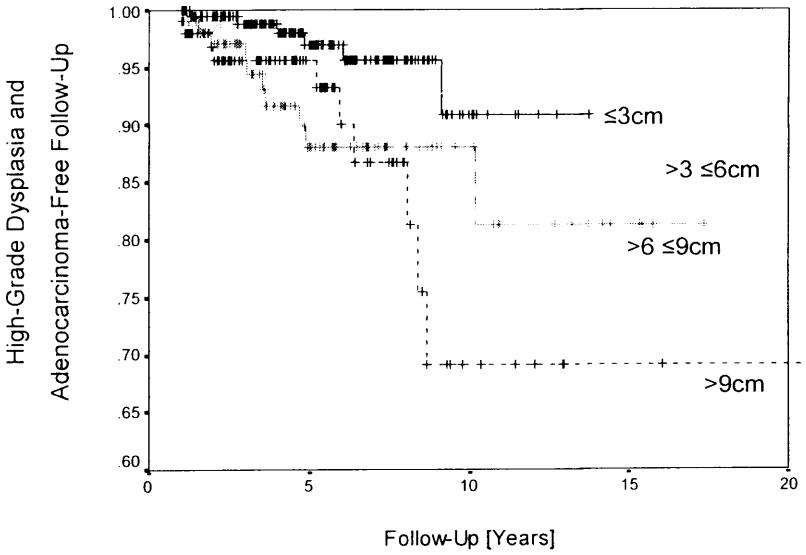


Figure 5.RF3 - Kaplan Meier Survival Plot for Development of Incident Adenocarcinoma Dependent on Diagnostic Histology

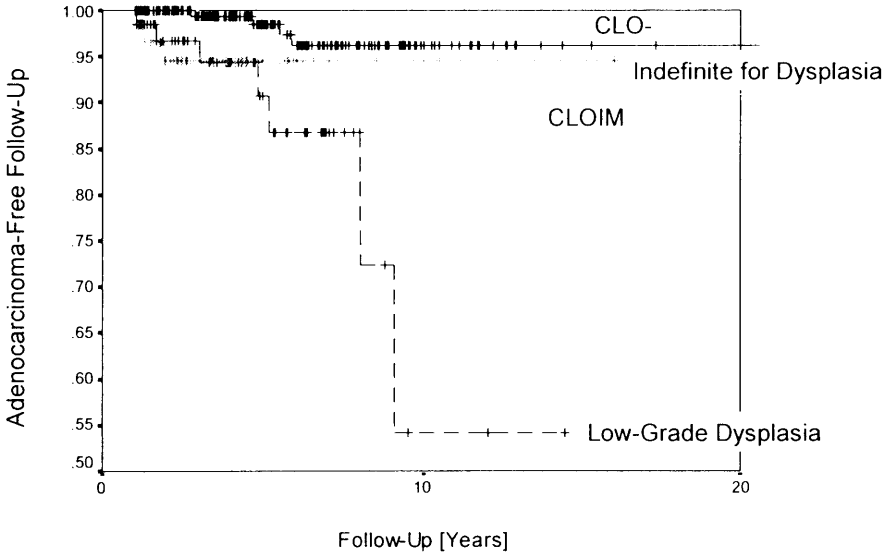
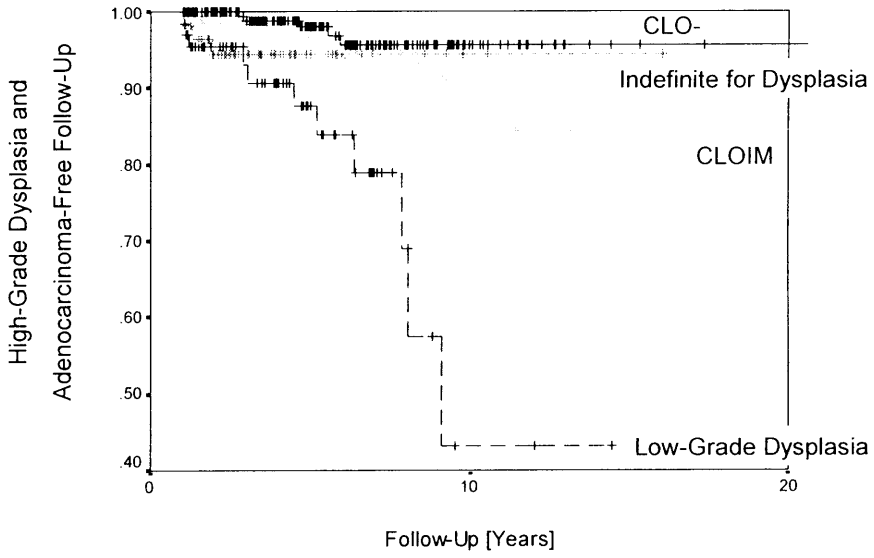


Figure 5.RF4 - Kaplan Meier Survival Plot for Development of Incident High-Grade Dysplasia or Adenocarcinoma Dependent on Diagnostic Histology



The annual incidence of adenocarcinoma in these patients dependent on segment length group is shown in table 5.RT7, and for diagnostic histology group is shown in table 5.RT8.

Table 5.RT7 - Annual Adenocarcinoma Incidence Dependent on Segment Length Group

Segment Length Group	N (%*) Patients	N (%†) Adenocarcinoma	Annual Adenocarcinoma Incidence	95% Confidence Interval‡
Segment ≤3cm	207 (29.2%)	6 (2.9%)	0.58%	0.21-1.27%
Segment >3 ≤6cm	282 (39.8%)	3 (1.1%)	0.21%	0.04-0.60%
Segment >6 ≤9cm	116 (16.4%)	7 (6.0%)	1.2%	0.47-2.42%
Segment >9cm	103 (14.5%)	6 (5.8%)	1.2%	0.45-2.67%
All Long Segment	501 (70.8%)	16 (3.2%)	0.62%	0.36-1.02%

* Percentage of total cohort
† Percentage of patients in segment length group
‡ Exact Poisson distribution

Table 5.RT8 - Annual Adenocarcinoma Incidence Dependent on Diagnostic Histology Group

Diagnostic Histology	N (%*) Patients	N (%†) Adenocarcinoma	Annual Adenocarcinoma Incidence	95% Confidence Interval‡
CLO-	236 (29.4%)	4 (1.7%)	0.32%	0.09-0.82%
CLOIM	439 (54.6%)	9 (2.1%)	0.42%	0.19-0.81%
Indefinite for Dysplasia	61 (7.6%)	3 (4.9%)	1.2%	0.25-3.60%
Low-Grade Dysplasia	68 (8.5%)	7 (10.3%)	2.3%	0.95-4.86%

* Percentage of total cohort
† Percentage of patients in diagnostic histology group
‡ Exact Poisson distribution

To allow for the confounding influence of age at diagnosis and diagnostic histology on adenocarcinoma dependent on segment length group, they were entered as covariates (with

gender and year of diagnosis) into the Cox proportional hazards analysis for development of adenocarcinoma (table 5.RT9) and high-grade dysplasia/adenocarcinoma (table 5.RT10).

Table 5.RT9 – Cox Proportional Hazards Analysis of Adenocarcinoma Incidence

Factor	P value	Odds Ratio	95% CI* for Odds Ratio
Gender (male/female)	0.590	1.288	0.513-3.236
Age at Diagnosis	0.002	1.090	1.033-1.151
Year of Diagnosis	0.194	0.930	0.832-1.038
CLOIM†	0.424	1.644	0.487-5.553
Indefinite for Dysplasia†	0.068	4.507	0.897-22.659
Low-Grade Dysplasia†	0.003	8.340	2.055-33.84
>3 ≤6cm‡	0.101	0.311	0.077-1.256
>6 ≤9cm‡	0.806	1.154	0.368-3.619
>9cm‡	0.810	0.861	0.253-2.928

* CI Confidence Interval
† Compared to columnar-lined oesophagus with no intestinal metaplasia, high-grade dysplasia excluded from table as only 3 patients fulfilled the criteria
‡ Compared to ≤3cm group

Table 5.RT10 – Cox Proportional Hazards Analysis of High-Grade Dysplasia or Adenocarcinoma Incidence

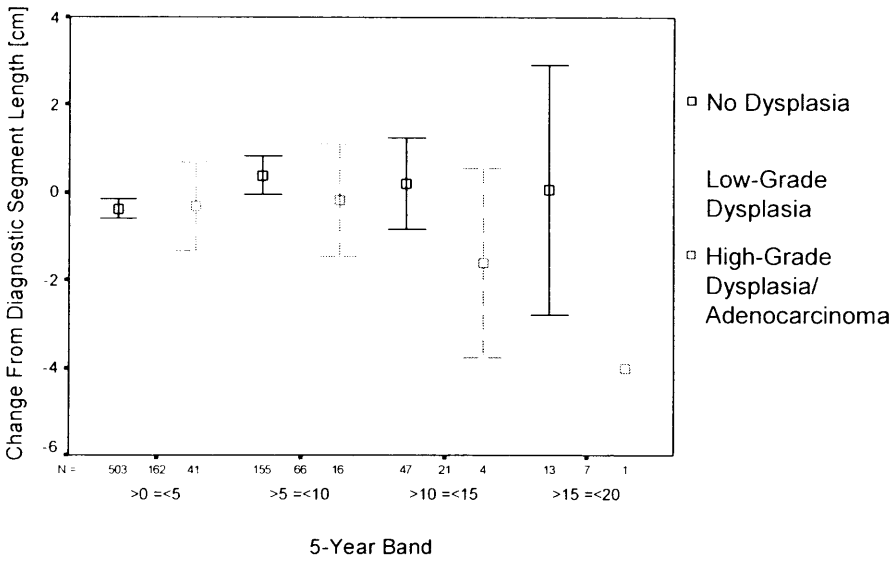
Factor	P value	Hazards Ratio	95% CI* for Hazards Ratio
Gender (male/female)	0.778	1.112	0.532-2.321
Age at Diagnosis	0.039	1.040	1.002-1.079
Year of Diagnosis	0.738	1.016	0.927-1.113
CLOIM†	0.087	2.627	0.868-7.948
Indefinite for Dysplasia†	0.121	3.406	0.723-16.04
Low-Grade Dysplasia†	<0.001	9.088	2.642-31.26
>3 ≤6cm‡	0.932	0.955	0.338-2.704
>6 ≤9cm‡	0.177	2.053	0.723-5.834
>9cm‡	0.169	2.116	0.727-6.162

* CI Confidence Interval
† Compared to columnar-lined oesophagus with no intestinal metaplasia
‡ Compared to ≤3cm group

Variability in Segment Length Measurement

There was no clear change in segment length when comparing the average segment length measured in five year bands following diagnosis – and the change from diagnostic length and 95% confidence interval for patients when grouped by most dysplastic histology (figure 5.RF5)

Figure 5.RF5 – Change From Diagnostic Segment Length Grouped by Most Dysplastic Histology Attained



ANOVA not significant for all groups

However, individual measurements did vary and this was examined in the 186 patients who had at least 3 segment length measurements. The median, quartile and 95th centile for the differences between the diagnostic segment length and the segment length furthest from the diagnostic length and for the differences between the mean segment length and the length furthest from mean segment length are shown in table 5.RT11.

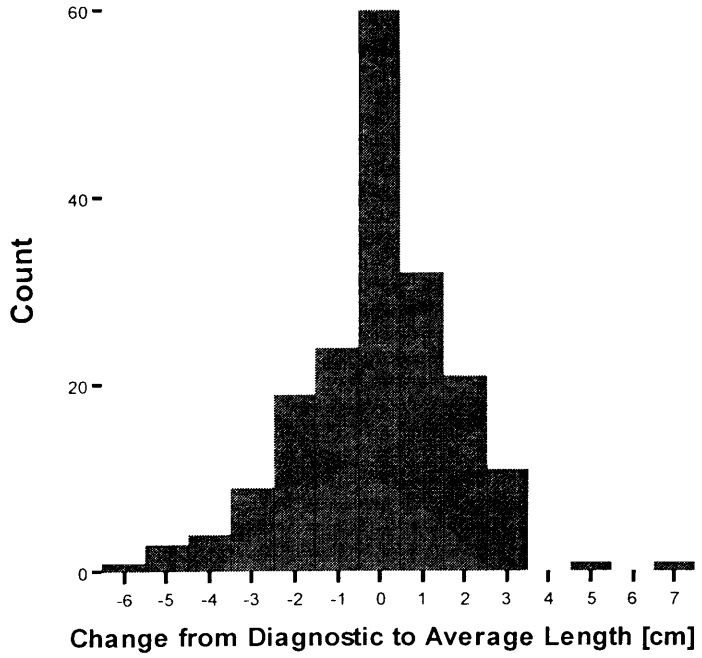
Table 5.RT11 – Median, Quartile and 95th Centile of Difference Between Furthest Outlying Segment Length and Diagnostic and Mean Segment Lengths

Centile	Change From Diagnostic Length [cm]	Change From Mean Length [cm]
25th	2.0	1.5
50th (median)	3.0	2.3
75th	5.0	3.5
95th	8.0	5.4

The difference between diagnostic segment length and mean segment length also varied, but the median change was 0.0cm. The 5% and 95% percentiles from change from

diagnostic length to mean length were -3.3cm and +3.1cm and the inter-quartile range was -1.0cm to +1.1cm. The histogram of changes from diagnostic to mean segment length is shown in figure 5.RF6.

Figure 5.RF6 – Histogram of Change from Diagnostic Segment Length to Mean Segment Length



Progression or Regression in Metaplastic Segment Length

Examining the patients for a progression or regression from diagnostic length to first 5-year band to second 5-year band, demonstrated that a progression was found in 28 of 186 patients (15.1%), and a regression in 24 (12.9%). There was no difference in maximum grade of dysplasia attained between patients who progressed, regressed or demonstrated no overall trend for a change in length.

Discussion and Conclusions

The greater levels of both acid and duodenal juice reflux[61-66] and more defective anti-reflux sphincter mechanism[60] associated with longer segments of columnar lined oesophagus would logically dictate that a clear risk should be apparent between metaplastic segment length and adenocarcinoma risk. This has been reported in a number of studies[61;87-89]. This study did demonstrate that both intestinal metaplasia (the mucosal subtype most frequently associated with adenocarcinoma[29;44-46;48-50;87;182-187]) and dysplasia were more common in longer segments of columnar-lined oesophagus. The age at columnar-lined oesophagus diagnosis was also higher in longer segment length groups (which has been demonstrated to be a risk for incident adenocarcinoma in chapter 4). However, as in the study of Rudolph *et al.*[90], there was no statistically significant association between incident adenocarcinoma (or high-grade dysplasia) risk and segment length. The risk of both incident adenocarcinoma (or high-grade dysplasia) and prevalent adenocarcinoma did tend to be higher in longer segments (>6cm) than either short (≤3cm) or intermediate (>3 ≤6cm) segments; and there was actually a trend for a lower risk in the intermediate length (>3 ≤6cm) segments. Overall, it must be noted that adenocarcinoma did develop in short (≤3cm) segment columnar-lined oesophagus and the risk in short-segment columnar-lined oesophagus (≤3cm) is the same as that in all long-segment (>3cm) disease. Consequently, this study would not support any determination of surveillance protocol based on segment length.

This study has also demonstrated that whilst overall segment length does not change for the entire cohort, there were a number of patients (28%) who appeared to progress or regress from the diagnostic length to the first and second 5-year bands after diagnosis. There was, however, a wide interobserver variability in segment length measurement, with half of the patients having a 3cm or more change from diagnostic length to the measurement furthest from this diagnostic length. Frequently, this may be due to discrepancies in interpretation of the endoscopic landmarks (due to tongues of columnar metaplasia above the metaplastic segment and hiatal hernia) rather than a true change in the metaplastic segment length. Examining the validity of the use of the first segment length to determine the segment length group into which the patient was categorized revealed only fair agreement (kappa coefficient 0.37). This would further discourage against the use of segment length to determine surveillance interval. Additionally, this study did not demonstrate that a

progression or regression in segment length is associated with a more benign or malignant histological outcome. Other studies have demonstrated that apparent regression of the metaplastic segment may be due to squamous epithelium overgrowing the underlying columnar mucosa[261;326] harbouring dysplasia[327] and adenocarcinoma[328]. Kim *et al.*[272] also demonstrated that in 53% of patients there was a discordance between an increase in measured segment length and decrease in calculated metaplastic segment area or vice-versa. Consequently, this study would not support the use of a change in segment length as a marker of increased or decreased malignant potential.

The study did not control for the biopsy protocol employed by the centres involved in the study, nor was there any means to corroborate histopathological diagnosis. Additionally, there was no control of the surveillance programmes which the centres involved based their practice on. Furthermore, the patchwork-nature of changes of intestinal metaplasia and dysplasia within the metaplastic segment render significant potential for sampling error[197;197;253-256;273]. Notwithstanding these potential sources of error, this cohort demonstrated a clear increased risk (8-fold) in adenocarcinoma (or high-grade dysplasia) with low-grade dysplasia over columnar-lined oesophagus without intestinal metaplasia. There was a trend for a higher risk in columnar-lined oesophagus with intestinal metaplasia (and no dysplasia) and columnar-lined oesophagus with indefinite changes for dysplasia over columnar-lined oesophagus with no intestinal metaplasia. These results are controlled for the confounding effect of age at diagnosis. Importantly, incident adenocarcinoma did develop in 4 patients (18% of all incident adenocarcinoma) who did not have intestinal metaplasia on diagnostic histology, and so would have been excluded from surveillance if the American College of Gastroenterology guidelines on the management of "Barrett's oesophagus" [91] were followed.

Chapter 6 – Histological Fate of the Metaplastic Segment over Time

Aims and Introduction

Columnar-Lined Oesophagus and Oesophageal Adenocarcinoma

Metaplastic columnar-lined oesophagus, originally described nearly 100 years ago[140] has been known to be associated with oesophageal adenocarcinoma for almost fifty years[41]. By the 1970s, this association had been strengthened by pathological studies demonstrating this metaplastic epithelium surrounding oesophageal adenocarcinomata[42-44], frequently with areas of dysplasia[22;29;44-49;49-51;184;185]. The major cause of these metaplastic and neoplastic changes is postulated to be prolonged gastro-oesophageal reflux[39;163]. This has been explored using animal models of gastro-oesophageal reflux[52;53] and reflux into the oesophagus of duodenal contents[55-58]. Studies from humans presenting with symptoms of gastro-oesophageal reflux have demonstrated that the acquisition of columnar metaplasia in the lower oesophagus occurs in patients with the most severe disease[59;61;66-68], and that reflux of duodenal contents (bile and pancreatic secretions) also plays an important role in the development of the disease[62-66]. The presence of columnar metaplasia of the oesophagus has been associated with a 5-125x increased risk of development of oesophageal adenocarcinoma when compared to a control population[86;89;92;168;169].

Purpose of Surveillance

The American College of Gastroenterology states: "The goal of surveillance in Barrett's esophagus is the detection of dysplasia and early cancer", and recommends surveillance "if there is a potential to prolong life expectancy with a therapeutic intervention for early cancer"[91]. However, the mortality of patients with columnar-lined oesophagus is no higher than that of control populations[86;89;221;230]. Adenocarcinomata detected within surveillance programmes are at an earlier stage than those diagnosed when they presented clinically[100-105], and have improved survival over cancers diagnosed outside of surveillance programmes[100;101;103-105], but are still frequently diagnosed at unscheduled extra surveillance endoscopies[230].

Dysplasia is the basis upon which surveillance frequency is determined[91]. The American College of Gastroenterology recommends surveillance practice based upon two endoscopies and surveillance interval based upon the absence or presence and grade of dysplasia[91]. For columnar-lined oesophagus with intestinal metaplasia, but no dysplasia: repeat endoscopy in 3 years. For findings of low-grade dysplasia: repeat endoscopy in 1 year. For findings of high-grade dysplasia: repeat endoscopy with an intensive biopsy protocol and confirmation by a second expert pathologist with consideration of intervention. In the case of multifocal high-grade dysplasia (involvement of 5 or more crypts or multiple biopsy specimens) or any visible lesion: immediate intervention. For focal high grade dysplasia (involving less than 5 crypts): repeat endoscopy in 3 months. The finding of high-grade dysplasia (and notably multifocal high-grade dysplasia) was considered (until recently) an indication for intervention due to the high probability of the presence of an occult adenocarcinoma; however one group has reported a low adenocarcinoma incidence in high-grade dysplasia (2.2% per annum)[277].

Risk Factors for Oesophageal Adenocarcinoma

A number of factors other than columnar metaplasia have been implicated as increasing the risk of oesophageal adenocarcinoma. Older age[24-27], male gender[4;6;23-25;27-29], white ethnicity[7;14;23;25;27;30-32], higher social class (in the UK)[4], alcohol consumption[31;33;34], cigarette smoking[24;31;33-36] and obesity[33;34;37;38] have all been associated with a higher risk of adenocarcinoma. Longer segments of columnarised segment have also been associated with a higher neoplastic risk than shorter segments[61;87-89]. However, the best current indicator of cancer risk is dysplasia of the metaplastic segment[91].

Progression of Columnar Metaplasia and Dysplasia to Adenocarcinoma

The overall rate of progression of columnar-lined oesophagus to oesophageal adenocarcinoma is 0.69% per annum (see appendix 1). Some series have reported adenocarcinoma only developing in patients who previously had changes of dysplasia in the metaplastic segment[92-94] and the American College of Gastroenterology only recommends surveillance of patients who are found to have goblet cell metaplasia within the metaplastic segment (as this is the epithelial subtype most frequently found surrounding

adenocarcinoma[29;44-46;48-50;87;182-187;252]). Patients who were first diagnosed with columnar-lined oesophagus without intestinal metaplasia have subsequently demonstrated intestinal metaplasia on further surveillance biopsies and later progressed to adenocarcinoma[87] and studies have suggested metaplastic pathways from squamous to cardiac to intestinal metaplasia[186;257]. However, neither the pathway of metaplasia involving gastric cardiac, gastric fundic and intestinal-type metaplasia, nor progression of low-grade or high-grade dysplasia is well defined. Skacel *et al.*[95] reported that the annual adenocarcinoma (or high-grade dysplasia) incidence in 25 patients with low-grade dysplasia was 12.9%, and Reid *et al.*[47] reported an annual adenocarcinoma incidence of 12% in 43 patients with low-grade dysplasia. Schnell *et al.*[277] followed-up 79 patients with high-grade dysplasia for 7.3 years, during which time the adenocarcinoma incidence was low: 2.2% in the first year and 2.1% per annum overall. Buttar *et al.*[97] found that overall 27.8% of patients in their cohort of 100 patients with high-grade dysplasia developed adenocarcinoma in the first year, and that the annual adenocarcinoma incidence over the first 3 years was 14.0%. Rudolph *et al.*[90] showed that the annual incidence of adenocarcinoma in patients with high-grade dysplasia was 23.0%, compared to 0.8% in patients without high-grade dysplasia at diagnosis.

Sampling Error and Interobserver Variability in Histological Interpretation

Studies have demonstrated that the prevalence of finding intestinal metaplasia increases with patient age[247;248], number of surveillance endoscopies[249], increased length of gastro-oesophageal reflux symptoms[250], increased oesophageal exposure to bile[250] and macroscopic length of columnarised segment[249;251]. The finding of goblet cells is subject to significant sampling error[197;253-255] and increases with the experience of the endoscopist[254] and number of biopsies taken from the metaplastic segment[256]. The finding of Nilsson *et al.*[87] of patients without intestinal metaplasia subsequently developing intestinal metaplasia and adenocarcinoma may have been (in part) due to sampling error. The area of dysplasia, and neoplasia in oesophagectomy specimens for high-grade dysplasia and early adenocarcinoma demonstrated that these only involved a small fraction of the total area of metaplastic epithelium[273].

A review of studies of oesophageal resection for the pre-operative finding of high-grade dysplasia demonstrated 80/184 (43%) patients had at least a focus of adenocarcinoma in the resected specimen[96]. A subsequent study showed an adenocarcinoma prevalence in 5/15

(33%) oesophagectomy specimens (resected for high-grade dysplasia)[274]. Two studies have demonstrated that the extent of high-grade dysplasia correlates with the probability of discovery of an occult carcinoma in the resected oesophagus at diagnosis of high-grade dysplasia or probability of one developing during follow-up[97;276]. Reid *et al.* [275] demonstrated that a 4-quadrant biopsy every 2 cm protocol would miss 13/26 (50%) of adenocarcinomata detected by a 4-quadrant biopsies taken every 1cm.

Interobserver agreement in histopathological interpretation of biopsy samples is subject to significant variability, most marked in the centre of the histological spectrum[281] (kappa values for: no dysplasia 0.44, indefinite for dysplasia 0.14, low-grade dysplasia 0.23, high-grade dysplasia 0.40, adenocarcinoma 0.67). Overall interobserver agreement is slight to fair (kappa 0.01 before a consensus meeting and 0.31 after the consensus meeting) when classifying slides into the 5 Vienna categories[189]; and moderate (kappa=0.43) when separating into no dysplasia, indefinite changes of dysplasia, low-grade dysplasia and the combined group of high-grade dysplasia and adenocarcinoma[189]. Comparing which patients demonstrate features of high-grade dysplasia and adenocarcinoma to those with no dysplasia, indefinite changes for dysplasia and low-grade dysplasia has yielded agreement of 85% and 87% on successive review of slides[280] and kappa values of 0.60 and 0.65 (moderate and substantial agreement) on successive review of slides[281]. In a study examining the outcome of low-grade dysplasia, the interobserver agreement between 3 pathologists for the diagnosis of low-grade dysplasia kappa value was 0.17 (slight agreement)[95]. A recent study[282] examined interobserver agreement between 2 gastrointestinal pathologists and one general pathologist on the diagnoses of high-grade dysplasia, intramucosal adenocarcinoma and invasive adenocarcinoma. They found that the overall agreement for these diagnoses was fair (kappa=0.59), and between the gastrointestinal pathologists agreement was good (kappa=0.68). Comparing high-grade dysplasia to intramucosal adenocarcinoma, the agreement between all pathologists was fair (kappa=0.42) and between gastrointestinal pathologists was also fair (kappa=0.56). Comparing high-grade dysplasia to submucosal adenocarcinoma was perfect (kappa=1.00) between all pathologists, and comparing intramucosal adenocarcinoma to submucosal carcinoma: agreement was good between all pathologists (kappa=0.71) and gastrointestinal pathologists (kappa=0.76).

Treatment of High-Grade Dysplasia and Early Adenocarcinoma

All of the adenocarcinomata which developed in a cohort of 79 patients with high-grade dysplasia were detected in a three monthly surveillance programme at a curable stage (with the exception of one in a patient who had defaulted follow-up)[277]. Romagnoli *et al.*[278] examined patients with high-grade dysplasia categorized into 3 groups: patients operated on immediately after the diagnosis, patients whose high-grade dysplasia persisted or progressed to adenocarcinoma at 6 months (and underwent oesophagectomy at that point) and the third group of patients who only underwent oesophagectomy when they had symptoms of dysphagia or biopsies demonstrated adenocarcinoma after 6 months (after high-grade dysplasia had been initially diagnosed). They demonstrated that the cancer-related survival was 100% in those operated-on immediately, but only 52.5% in those surveyed for 6 months or more and advised oesophagectomy as the treatment of choice in high-grade dysplasia.
The American College of Gastroenterology practice guidelines recommend intervention for multifocal (involvement of more than 5 crypts) high-grade dysplasia corroborated by a second specialist gastrointestinal pathologist with oesophagectomy, endoscopic mucosal resection or endoscopic ablation.
The current UK guidelines on the management of oesophageal and gastric cancers recommend that in the case of high-grade dysplasia - urgent review of endoscopy with repeat biopsy is undertaken, then careful consideration should be given to resection[279].

Adenocarcinomata which have invaded to the level of the submucosa have a much greater risk of lymph-node metastases, than more superficial lesions (intramucosal adenocarcinoma and high-grade dysplasia)[71;108;110] necessitating a more radical approach to resection than treatment of the mucosa only. Superficial lesions may be treated by surgical resection[108;279], endoluminal ablation (using thermal or photodynamic modalities)[113-115] or endoluminal resection[116;307] (or a combination of these treatments to remove specific lesions and destroy the remaining metaplastic segment[293;294]).

Subsequently, patients with columnar-lined oesophagus may be surveyed in an attempt to identify dysplasia and adenocarcinoma before the lesion becomes incurable, with surveillance programmes[87;100;103;183;244;245] based around the guidelines of the American

College of Gastroenterology[91]. This chapter examines the natural history of the histology findings of the metaplastic segment.

Methods

This study includes patients who had been diagnosed with columnar-lined oesophagus at 7 centres throughout the UK. The patients were all registered with UKBOR, and were involved with an in-depth analysis on the natural history of columnar-lined oesophagus. Three registry researchers visited the centres involved and extracted information from patients' hospital records – typically including endoscopy, histology and operation reports, correspondence following outpatient attendances and inpatient stays. The data were entered into a Microsoft Access database[321], which allowed storage and selection of patients for inclusion in the analyses. Patients from the 7 centres were included in the analyses of changes in segment histology and differences in adenocarcinoma risk dependent on histology if they fulfilled criteria, which were based around the analyses performed. The natural history of metaplastic and dysplastic changes were analysed over the entire period of histological follow-up of the metaplastic segment, as opposed to the earlier chapters which examined outcome (development of high-grade dysplasia or adenocarcinoma) dependent on the diagnostic histological biopsies. The results are presented as survival analyses, with survival tables (which state the fraction of patients "surviving" i.e. not developing the end-point histology changes at 6 months, 1 year, 2 years, 3 years, 5 years and 10 years) to allow comparisons of the rate of detection of patients progressing to dysplasia and adenocarcinoma at different follow-up periods.
For analysis of development of dysplasia and adenocarcinoma, patients were grouped into the 5 Vienna classification categories[189], with the addition of a further group, separating non-dysplastic columnar-lined oesophagus into patients without evidence of intestinal metaplasia and those with intestinal metaplasia (table 6.MT1).

Table 6.MT1 – Histology Groups

Histology Group	Description
CLO-	Columnar-lined oesophagus without intestinal metaplasia or dysplasia
CLOIM	Columnar-lined oesophagus with intestinal metaplasia and without dysplasia
Indefinite for dysplasia	Columnar-lined oesophagus with changes indefinite for dysplasia
LGD	Columnar-lined oesophagus with low-grade dysplasia
HGD	Columnar-lined oesophagus with high-grade dysplasia
AC	Adenocarcinoma

Patient Selection

Patients were selected in all of the analyses in this chapter if they had at least one histology report demonstrating columnar-lined oesophagus.

For analysis of low-grade dysplasia, high-grade dysplasia and adenocarcinoma incidence dependent on presence of metaplasia and dysplasia:

1. Only patients who had a biopsy demonstrating the specified "entry" histology (the first histological evidence of the specified histology group, which had not been preceded by more dysplastic histology findings)
2. Patients had at least one further biopsy demonstrating columnar-lined oesophagus, but there was no minimum time requirement from the "entry histology" biopsy to the last biopsy

For analysis of variability of the finding of intestinal metaplasia over time:

1. Only patients who had a diagnostic biopsy demonstrating columnar-lined oesophagus without indefinite changes for dysplasia, dysplasia or adenocarcinoma
2. For analysis on the influence of number of pieces of tissue examined by the histopathologist, this had to be stated on either the endoscopy or histology report and if a discrepancy existed between these values then the stated number of tissue fragments on the histology report was used

3. For analysis of the influence of segment length on the finding of intestinal metaplasia in the non-dysplastic segment, a metaplastic segment length measured from the squamocolumnar junction to the gastro-oesophageal junction was required

The date of diagnosis was considered to be the first histological confirmation of columnar-lined oesophagus and date of "entry" for a histology group was first finding of that grade of metaplasia/dysplasia (without more dysplastic histology found previously or concurrently).

The overall rates of progression to columnar-lined oesophagus with intestinal metaplasia, low-grade dysplasia, high-grade dysplasia and adenocarcinoma were examined using Kaplan-Meier survival analysis, and comparisons between groups were made using Cox's proportional hazards ratio analysis with covariates of gender, age at diagnosis and year of diagnosis. Proportional hazards ratios were evaluated between each pair of "entry histology" groups. For analysis of development of intestinal metaplasia, the number of pieces of biopsy tissue and first recorded segment length (where this was available) were also entered as covariates into the analysis

- The follow-up period was defined as the period from the first histology report demonstrating the specified "entry" histology, and terminated at the earliest biopsy demonstrating the specified "target" histology or histology demonstrating more dysplastic features than this "target" histology, or (if this was not attained) then the final histology report
- If patients underwent an intervention to the metaplastic segment, (oesophagectomy, endoscopic mucosal resection or ablation) then they were censored at the date of the histological report immediately preceding the intervention
- The proportion of patients remaining free of intestinal metaplasia, low-grade dysplasia, high-grade dysplasia and adenocarcinoma is stated in survival tables and results were censored when 5 or fewer patients remained in the analysis
- Projected results beyond the longest follow-up period in each cohort (or 20 years, whichever was shorter) are not estimated

To analyse the probability of the finding of intestinal metaplasia within the columnarised segment, patients without dysplasia, adenocarcinoma or indefinite changes for dysplasia

were examined. Logistic regression was undertaken of all of the histology reports using the covariates of patient age at the biopsy, gender, number of samples of biopsy tissue received and examined by the histopathologist (where available), and first measured segment length of metaplastic epithelium (where available). Logistic regression was performed and repeated without the covariates of number of tissue samples and segment lengths as this information was not available for all patients. The number of histology reports in patients who did/did not demonstrate intestinal metaplasia in non-dysplastic columnar metaplasia was compared using independent t-test.

Results

Histological Outcome Dependent on "Entry" Histology

Of the whole cohort of patients involved in the study, the following numbers of patients were available for the analyses (table 6.RT1):

Table 6.RT1 – Patients Included in the Analyses of Histological Outcome

Entry Histology	Number of Patients
Columnar-Lined Oesophagus Without Intestinal Metaplasia	322
Columnar-Lined Oesophagus With Intestinal Metaplasia	612
Indefinite Changes for Dysplasia	144
Low-Grade Dysplasia	212
High-Grade Dysplasia	39

The median and maximum follow-up period for each "entry" histology cohort are shown in table 6.RT2.

Table 6.RT2 – Median and Maximum Follow-Up Time for Each "Entry" Histology Cohort

Entry Histology	Median Follow-Up*	Maximum Follow-Up*
CLO-†	3.49	20.79
CLOIM†	3.55	22.90
Indefinite†	2.81	16.04
LGD†	1.98	14.47
HGD†	0.36	8.94

* Follow-up measured in years
† CLO- Columnar-Lined Oesophagus without Intestinal Metaplasia
† CLOIM Columnar-Lined Oesophagus with Intestinal Metaplasia
† Indefinite Indefinite Changes for Dysplasia
† LGD Low-Grade Dysplasia
† HGD High-Grade Dysplasia

The proportions of patients developing the "target" histology dependent on each "entry" histology at 6 months, 1 year, 2 years, 3 years, 5 years and 10 years are shown in the

survival tables 6.RT3-6.RT7, and median time, quartiles and 90th and 10th centiles are shown in tables 6.RT8-6.RT12.

Columnar-lined oesophagus initially not demonstrating intestinal metaplasia has a very low malignant potential, with less than 10% of patients developing adenocarcinoma at follow-up of 20 years. However, 10% of patients had developed dysplasia at 3.1 years of follow-up, and 90% had demonstrated features of intestinal metaplasia within 9.3 years (tables 6.RT3 and 6.RT8). In patients with columnar-lined oesophagus with intestinal metaplasia, adenocarcinoma was still a rare occurrence, but 10% of patients had developed high-grade dysplasia or adenocarcinoma at 10 years of follow-up, and 25% had developed dysplasia at 5.1 years of follow-up (tables 6.RT4 and 6.RT9). Unfortunately, the sizes of the cohorts with changes indefinite for dysplasia and high-grade dysplasia are small and follow-up was shorter. However, the patients with changes indefinite for dysplasia behaved similarly to those with columnar-lined oesophagus with intestinal metaplasia (tables 6.RT5 and 6.RT10); and the median time for adenocarcinoma to be found in high-grade dysplasia was 0.6 years (tables 6.RT7 and 6.RT12). Patients with low-grade dysplasia progressed to high-grade dysplasia and adenocarcinoma over a median of 9.8 years (table 6.RT11). Three percent of these patients progressed to adenocarcinoma within one year (table 6.RT6).

Table 6.RT3 – Survival Table for Patients Remaining Free of the Development of Intestinal Metaplasia, Dysplasia and Adenocarcinoma Following the Finding of Columnar-Lined Without Intestinal Metaplasia

Target Histology	% at 6 months*	% at 1 year*	% at 2 years*	% at 3 years*	% at 5 years*	% at 10 years*
CLOIM†	87.3%	77.4%	59.0%	45.2%	28.0%	9.2%
Indefinite†	94.8%	92.3%	89.2%	82.6%	72.7%	50.9%
LGD†	96.7%	95.7%	94.1%	90.1%	85.4%	64.8%
HGD†	97.7%	97.7%	97.7%	96.7%	95.9%	93.8%
AC†	98.0%	98.0%	98.0%	97.5%	96.7%	94.6%

* % of Patients who have not developed target histology changes or changes of greater dysplasia
† CLOIM Columnar-Lined Oesophagus with Intestinal Metaplasia
† Indefinite Indefinite Changes for Dysplasia
† LGD Low-Grade Dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma

Table 6.RT4 – Survival Table for Patients Remaining Free of the Development of Dysplasia and Adenocarcinoma Following the Finding of Columnar-Lined With Intestinal Metaplasia

Target Histology	% at 6 months*	% at 1 year*	% at 2 years*	% at 3 years*	% at 5 years*	% at 10 years*
Indefinite†	94.5%	92.0%	84.2%	77.1%	62.8%	39.7%
LGD†	96.0%	94.4%	90.9%	86.6%	76.2%	60.7%
HGD†	97.8%	97.5%	97.1%	96.6%	95.2%	91.1%
AC†	98.5%	98.1%	97.9%	97.7%	96.6%	93.5%

* % of Patients who have not developed target histology changes or changes of greater dysplasia
† Indefinite Indefinite Changes for Dysplasia
† LGD Low-Grade Dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma

Table 6.RT5 – Survival Table for Patients Remaining Free of the Development of Dysplasia and Adenocarcinoma Following the Finding of Indefinite Changes for Dysplasia

Target Histology	% at 6 months*	% at 1 year*	% at 2 years*	% at 3 years*	% at 5 years*	% at 10 years*
LGD†	97.9%	94.8%	80.0%	71.4%	62.8%	-‡
HGD†	99.3%	99.3%	93.9%	93.9%	93.9%	-‡
AC†	99.3%	99.3%	94.8%	94.8%	94.8%	-‡

* % of Patients who have not developed target histology changes or changes of greater dysplasia
† LGD Low-Grade Dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma
‡ Less than 5 patients remained at 10 years, so results censored

Table 6.RT6 – Survival Table for Patients Remaining Free of the Development of High-Grade Dysplasia and Adenocarcinoma Following the Finding of Low-Grade Dysplasia

Target Histology	% at 6 months*	% at 1 year*	% at 2 years*	% at 3 years*	% at 5 years*	% at 10 years*
HGD†	94.5%	93.9%	91.6%	90.6%	89.4%	50.7%
AC†	97.5%	96.9%	95.3%	95.3%	92.2%	58.3%

* % of Patients who have not developed target histology changes or changes of greater dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma

Table 6.RT7 – Survival Table for Patients Remaining Free of the Development of Adenocarcinoma Following the Finding of High-Grade Dysplasia

Target Histology	% at 6 months	% at 1 year	% at 2 years	% at 3 years	% at 5 years	% at 10 years
AC†	58.2%	49.6%	32.9%	-‡	-‡	-‡

† AC Adenocarcinoma
‡ Less than 5 patients remained at 3 years, so results censored from this point onwards

Table 6.RT8 – Median Time to Develop Intestinal Metaplasia, Dysplasia and Adenocarcinoma Following the Finding of Columnar-Lined Oesophagus without Intestinal Metaplasia

Target Histology	90th Centile*	75th Centile*	Median*	25th Centile*	10th Centile*
CLOIM†	0.2	0.9	2.3	5.4	9.3
Indefinite†	1.5	4.5	9.9	-‡	-§
LGD†	3.1	6.5	-‡	-§	-§
HGD†	-§	-§	-§	-§	-§
AC†	-§	-§	-§	-§	-§

* Time [Years] for patients remaining in cohort who had not attained target histology changes or changes of greater dysplasia
† CLOIM Columnar-Lined Oesophagus with Intestinal Metaplasia
† Indefinite Indefinite Changes for Dysplasia
† LGD Low-Grade Dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma
‡ Less than 5 patients remained at this centile point, so results censored from this point onwards
§ Centile point not reached in cohort within 20 years of follow-up

Table 6.RT9 – Median Time to Develop Dysplasia and Adenocarcinoma Following the Finding of Columnar-Lined Oesophagus with Intestinal Metaplasia

Target Histology	90th Centile*	75th Centile*	Median*	25th Centile*	10th Centile*
Indefinite†	1.0	3.1	8.0	-‡	-§
LGD†	1.9	5.1	-‡	-§	-§
HGD†	10.0	-§	-§	-§	-§
AC†	-§	-§	-§	-§	-§

* Time [Years] for patients remaining in cohort who had not attained target histology changes or changes of greater dysplasia
† Indefinite Indefinite Changes for Dysplasia
† LGD Low-Grade Dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma
‡ Less than 5 patients remained at this centile point, so results censored from this point onwards
§ Centile point not reached in cohort within 20 years of follow-up

Table 6.RT10 – Median Time to Develop Dysplasia and Adenocarcinoma Following the Finding of Changes Indefinite for Dysplasia

Target Histology	90th Centile*	75th Centile*	Median*	25th Centile*	10th Centile*
LGD†	1.1	2.1	8.2	-§	-§
HGD†	-§	-§	-§	-§	-§
AC†	-§	-§	-§	-§	-§

* Time [Years] for patients remaining in cohort who had not attained target histology changes or changes of greater dysplasia
† LGD Low-Grade Dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma
§ Centile point not reached in cohort within 16 years of follow-up (maximum follow-up for this entry histology)

Table 6.RT11 – Median Time to Develop High-Grade Dysplasia and Adenocarcinoma Following the Finding of Low-Grade Dysplasia

Target Histology	90th Centile*	75th Centile*	Median*	25th Centile*	10th Centile*
HGD†	2.9	7.9	9.8	-§	-§
AC†	5.0	8.9	-§	-§	-§

* Time [Years] for patients remaining in cohort who had not attained target histology changes or changes of greater dysplasia
† HGD High-Grade Dysplasia
† AC Adenocarcinoma
§ Centile point not reached in cohort within 14 years of follow-up (maximum follow-up for this entry histology)

Table 6.RT12 – Median Time to Develop Adenocarcinoma Following the Finding of High-Grade Dysplasia

Target Histology	90th Centile*	75th Centile*	Median*	25th Centile*	10th Centile*
AC†	0.0	0.1	0.6	-§	-§

* Time [Years] for patients remaining in cohort who had not attained target histology changes
† AC Adenocarcinoma
§ Centile point not reached in cohort within 9 years of follow-up (maximum follow-up for this entry histology)

Hazards Analysis of Risk of Dysplasia and Adenocarcinoma Development

Columnar-Lined Oesophagus without Intestinal Metaplasia Compared to All Other "Entry Histology" Groups

The proportional hazards ratio between columnar-lined oesophagus without intestinal metaplasia and the other histological groups are listed in tables 6.RT13-6.RT16. As would be expected, the hazard of development of changes of high-grade dysplasia or adenocarcinoma were much greater in patients whose biopsies had demonstrated dysplasia (low-grade dysplasia for the development of high-grade dysplasia and either low or high-grade dysplasia for the development of adenocarcinoma) compared to those with non-dysplastic columnar metaplasia without features of intestinal metaplasia (tables 6.RT15 and 6.RT16). Patients with changes indefinite for dysplasia had an increased hazard of developing changes of low-grade dysplasia (or more dysplastic histology), but there was no significant difference when examining for the development of high-grade dysplasia or adenocarcinoma only (table 6.RT14). Comparing non-dysplastic columnar-lined oesophagus without intestinal metaplasia to non-dysplastic columnar-lined oesophagus with intestinal metaplasia, there was an increased hazard of developing changes indefinite for dysplasia (or more dysplastic histology) in the patients who had intestinal metaplasia, but only a trend for dysplasia or adenocarcinoma (table 6.RT13).

Table 6.RT13 – Proportional Hazards Ratios Comparing Development of Dysplasia and Adenocarcinoma between Columnar-Lined Oesophagus without Intestinal Metaplasia and Columnar-Lined Oesophagus with Intestinal Metaplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
Indefinite Changes for Dysplasia†	0.039	1.313	1.014-1.699
Low-Grade Dysplasia†	0.069	1.366	0.976-1.911
High-Grade Dysplasia†	0.290	1.444	0.730-2.856
Adenocarcinoma	0.431	1.364	0.629-2.957

* Hazard comparing columnar-lined oesophagus with intestinal metaplasia to reference category of columnar-lined oesophagus without intestinal metaplasia
† Or changes of greater dysplasia or adenocarcinoma

Table 6.RT14 – Proportional Hazards Ratios Comparing Development of Dysplasia and Adenocarcinoma between Columnar-Lined Oesophagus without Intestinal Metaplasia and Columnar-Lined Oesophagus with Indefinite Changes for Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
Low-Grade Dysplasia†	<0.001	2.610	1.715-3.973
High-Grade Dysplasia†	0.248	1.773	0.671-4.684
Adenocarcinoma	0.159	2.161	0.739-6.319

* Hazard comparing columnar-lined oesophagus with indefinite changes for dysplasia to reference category of columnar-lined oesophagus without intestinal metaplasia
† Or changes of greater dysplasia or adenocarcinoma

Table 6.RT15 – Proportional Hazards Ratios Comparing Development of High-Grade Dysplasia and Adenocarcinoma between Columnar-Lined Oesophagus without Intestinal Metaplasia and Low-Grade Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
High-Grade Dysplasia†	<0.001	4.506	2.160-9.399
Adenocarcinoma	0.002	3.847	1.606-9.214

* Hazard comparing low-grade dysplasia to reference category of columnar-lined oesophagus without intestinal metaplasia
† Or adenocarcinoma

Table 6.RT16 – Proportional Hazards Ratios Comparing Development of Adenocarcinoma between Columnar-Lined Oesophagus without Intestinal Metaplasia and High-Grade Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
Adenocarcinoma	<0.001	48.383	20.483-114.289

* Hazard comparing high-grade dysplasia to reference category of columnar-lined oesophagus without intestinal metaplasia

Columnar-Lined Oesophagus with Intestinal Metaplasia Compared to All Other "Entry Histology" Groups

The proportional hazards ratios of development of the "target histology" comparing columnar-lined oesophagus with intestinal metaplasia to the other "entry histology" groups are shown in tables 6.RT13 and 6.RT17-6.RT19. Indefinite changes for dysplasia had a greater hazard of developing low-grade dysplasia (or more dysplastic histology, but only a trend for high-grade dysplasia or adenocarcinoma (table 6.RT17)). The hazards ratios for developing high-grade dysplasia or adenocarcinoma were significantly higher for "entry histology" diagnoses of low-grade dysplasia or high-grade dysplasia when compared to columnar-lined oesophagus with intestinal metaplasia (tables 6.RT18 and 6.RT19).

Table 6.RT17 – Proportional Hazards Ratios Comparing Development of Dysplasia and Adenocarcinoma between Columnar-Lined Oesophagus with Intestinal Metaplasia and Columnar-Lined Oesophagus with Indefinite Changes for Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
Low-Grade Dysplasia†	<0.001	1.965	1.388-2.783
High-Grade Dysplasia†	0.654	1.209	0.528-2.768
Adenocarcinoma	0.329	1.579	0.631-3.953

* Hazard comparing columnar-lined oesophagus with indefinite changes for dysplasia to reference category of columnar-lined oesophagus with intestinal metaplasia
† Or changes of greater dysplasia or adenocarcinoma

Table 6.RT18 – Proportional Hazards Ratios Comparing Development of High-Grade Dysplasia and Adenocarcinoma between Columnar-Lined Oesophagus with Intestinal Metaplasia and Low-Grade Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
High-Grade Dysplasia†	<0.001	3.166	1.810-5.538
Adenocarcinoma	0.003	2.945	1.456-5.958

* Hazard comparing low-grade dysplasia to reference category of columnar-lined oesophagus with intestinal metaplasia
† Or adenocarcinoma

Table 6.RT19 – Proportional Hazards Ratios Comparing Development of Adenocarcinoma between Columnar-Lined Oesophagus with Intestinal Metaplasia and High-Grade Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
Adenocarcinoma	<0.001	33.237	16.942-65.205

* Hazard comparing high-grade dysplasia to reference category of columnar-lined oesophagus with intestinal metaplasia

Columnar-Lined Oesophagus with Indefinite Changes for Dysplasia Compared to All Other "Entry Histology" Groups

The proportional hazards ratios of development of the "target histology" comparing columnar-lined oesophagus with indefinite changes for dysplasia to the other "entry histology" groups are shown in tables 6.RT14, 6.RT17, 6.RT20 and 6.RT21. There was an increased hazard of development of high-grade dysplasia or adenocarcinoma in patients with low-grade dysplasia, but not development of adenocarcinoma alone (table 6.RT20). High-grade dysplasia also had a significantly greater hazard of adenocarcinoma development (table 6.RT21).

Table 6.RT20 – Proportional Hazards Ratios Comparing Development of High-Grade Dysplasia and Adenocarcinoma between Columnar-Lined Oesophagus with Indefinite Changes for Dysplasia and Low-Grade Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
High-Grade Dysplasia†	0.026	2.632	1.125-6.158
Adenocarcinoma	0.191	1.901	0.726-4.975

* Hazard comparing low-grade dysplasia to reference category of columnar-lined oesophagus with indefinite changes for dysplasia
† Or adenocarcinoma

Table 6.RT21 – Proportional Hazards Ratios Comparing Development of Adenocarcinoma between Columnar-Lined Oesophagus with Indefinite Changes for Dysplasia and High-Grade Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
Adenocarcinoma	<0.001	21.266	9.297-54.502

* Hazard comparing high-grade dysplasia to reference category of columnar-lined oesophagus with indefinite changes for dysplasia

Columnar-Lined Oesophagus with Low-Grade Dysplasia Compared to All Other "Entry Histology" Groups

The proportional hazards ratios of development of the "target histology" groups comparing columnar-lined oesophagus with low-grade dysplasia to the other "entry histology" groups are shown in tables 6.RT15, 6.RT18, 6.RT20 and 6.RT22. The hazard of adenocarcinoma development with the "entry histology" of high-grade dysplasia is significantly greater than with low-grade dysplasia.

Table 6.RT22 – Proportional Hazards Ratios Comparing Development of Adenocarcinoma between Columnar-Lined Oesophagus with Low-Grade Dysplasia and High-Grade Dysplasia

"Target Histology"	p Value	Proportional Hazards Ratio*	95% CI for Hazards Ratio
Adenocarcinoma	<0.001	15.783	7.406-33.635

* Hazard comparing high-grade dysplasia to reference category of low-grade dysplasia

Analysis of Presence of Intestinal Metaplasia in Non-Dysplastic Metaplastic Columnar-Lined Oesophagus

The finding of intestinal metaplasia in non-dysplastic columnar epithelium was analysed in 3568 biopsies from 1751 patients. Of these, 2347 (65.8%) demonstrated intestinal metaplasia and 1221 (34.2%) did not demonstrate intestinal metaplasia. Two thousand nine hundred and forty seven had the number of samples of biopsy tissue examined stated on the histopathology report, 2724 had a segment length stated on an endoscopy report and 2233 had both the number of samples of tissue and segment length recorded. Excluding segment length and number of samples of biopsy tissue, the finding of intestinal metaplasia correlated with gender (odds ratio for males compared to females=1.435, 95% confidence interval 1.238-1.663, p<0.001) and age at which the biopsy was taken (for each increased year of age odds ratio=1.010, 95% confidence interval 1.004-1.015, p=0.001). Both the number of tissue samples (odds ratio per unit increase in number of tissue pieces=1.260, 95% confidence interval 1.197-1.327, p<0.001) and first recorded segment length (odds ratio per centimetre increase in diagnostic segment length=1.104, 95% confidence interval

1.071-1.137, p<0.001) also correlated with the probability of intestinal metaplasia detection. When all four variables were included in the analysis, gender became a less important factor and age at biopsy did not reach statistical significance, whilst both number of biopsy tissue samples taken and segment length still remained highly significant. The outcome of the logistic regression involving all 4 covariates is shown in table 6.RT23.

Table 6.RT23 – Odds Ratio of Finding of Intestinal Metaplasia in Non-Dysplastic Columnar-Lined Oesophagus Dependent on Gender, Patient Age, Number of Pieces of Biopsy Tissue and First Recorded Segment Length

Factor	P Value	Odds Ratio	95% CI* for Odds Ratio
Gender (Male/Female)	0.031	1.244	1.020-1.518
Age at Biopsy [Years]	0.438	1.003	0.995-1.011
First Segment Length [cm]	<0.001	1.103	1.065-1.142
Number of Samples of Tissue	<0.001	1.240	1.166-1.318

*CI Confidence Interval

When the number of histology reports was analysed, the odds ratio of finding intestinal metaplasia per unit increase in number of reports was 1.926 (95% confidence interval 1.694-2.194, p<0.001). Four hundred and forty three of the 486 patients (91.2%) who did not have intestinal metaplasia in their non-dysplastic biopsies had only one or two sets of samples taken. Of the patients who did demonstrate intestinal metaplasia in non-dysplastic columnar-lined oesophagus, 144 (11.4%) had 5 or more histology reports, compared to 6 patients (1.2%) who did not demonstrate intestinal metaplasia. The mean number of biopsy samples in patients who demonstrated intestinal metaplasia was 2.29, and in patients who did not demonstrate intestinal metaplasia was 1.37 (independent t-test p<0.001, but sample variances were not equal).

Discussion and Conclusions

Risk of Dysplasia and Adenocarcinoma Dependent on Histological Findings

This study has demonstrated that the risk of development of high-grade dysplasia and adenocarcinoma is low in non-dysplastic columnar-lined oesophagus. Kaplan-Meier survival analysis demonstrated that less than 10% of patients with non-dysplastic columnar-lined oesophagus develop high-grade dysplasia or adenocarcinoma within 10 years of their first biopsy demonstrating metaplastic columnar epithelium (with or without intestinal metaplasia). Less than 10% of patients with indefinite changes for dysplasia had developed high-grade dysplasia or adenocarcinoma within 5 years, but the cohort did not have sufficient power to evaluate these patients at 10 years of follow-up. Similar proportions of patients in the non-dysplastic group without intestinal metaplasia and with intestinal metaplasia developed low-grade dysplasia at 3, 5 and 10 years, and there was no difference between these two groups in development of dysplasia or adenocarcinoma when evaluated using Cox's proportional hazards analysis. Comparing indefinite changes of dysplasia to either columnar-lined oesophagus without intestinal metaplasia or with intestinal metaplasia revealed an increased hazard of development of low-grade dysplasia, but no significant difference in development of high-grade dysplasia or adenocarcinoma.
The finding of low-grade dysplasia was associated with an increased hazard of development of high-grade dysplasia and adenocarcinoma over non-dysplastic columnar-lined oesophagus, with a hazard ratio of 2.6 to 4.5 (higher when compared to columnar-lined oesophagus without intestinal metaplasia compared to columnar-lined oesophagus with intestinal metaplasia over indefinite changes for dysplasia). At one year, over half of the patients (followed-up to this point) with high-grade dysplasia had developed adenocarcinoma. The hazards ratio of development of adenocarcinoma following the finding of high-grade dysplasia was statistically higher than the finding of low-grade dysplasia or non-dysplastic columnar-lined oesophagus with a hazards ratio of 15.8-48.4.

Comparison of This Study's Findings with The American College of Gastroenterology Surveillance Guidelines

The American College of Gastroenterology guidelines on the management of columnar-lined oesophagus[91] do not recommend surveillance of metaplastic columnar epithelium without intestinal metaplasia. The study reported here found that of these patients, 4.1% had developed high-grade dysplasia or adenocarcinoma at 5 years and 6.2% at 10 years. If these patients were not undergoing surveillance, then if adenocarcinoma did develop it would be likely to present at a late stage[100-105] and have a worse survival rate than if detected within a surveillance programme[100;101;103-105]. Furthermore, low-grade dysplasia would not have been detected in the 10% of patients developing these changes at 5 years, with particular potential for these patients to develop changes of further dysplasia subsequently.

The guidelines[91] recommend surveillance endoscopy and systematic biopsy of patients with non-dysplastic columnar epithelium with intestinal metaplasia at 3 years following the initial diagnosis (and a repeated endoscopy with further systematic biopsies). Study of this cohort demonstrated that 10.0% of these patients had developed low-grade dysplasia at 3 years, and 3.4% had developed high-grade dysplasia or adenocarcinoma at this time. If the surveillance interval had been 2 years, 6.2% would have developed low-grade dysplasia, and 2.9% high-grade dysplasia or adenocarcinoma and surveillance at one year would yield 5.6% of patients developing dysplasia within this period and 1.9% adenocarcinoma. Patients with changes interpreted as being indefinite for dysplasia had an increased hazard of development of low-grade dysplasia when compared to non-dysplastic columnar-lined oesophagus either with or without intestinal metaplasia, but no significantly increased hazard in the development of high-grade dysplasia or adenocarcinoma. This is discussed in the subsection on sources of error in this data at the end of the discussion. At 3 years, 23.4% of these patients with indefinite changes for dysplasia had developed changes of dysplasia, but only 5.2% adenocarcinoma. At 2 years, the figures are 14.8% for dysplasia and the same fraction for adenocarcinoma; and at one year, only 4.5% had developed dysplasia and 0.7% had developed adenocarcinoma. Currently, the American College of Gastroenterology would group these patients with those with intestinal metaplasia, but no dysplasia (and repeat surveillance at 3 years). If the goal of surveillance was purely to detect high-grade dysplasia or adenocarcinoma, then managing the surveillance of these

patients with indefinite changes of dysplasia with those with no dysplasia is appropriate, but for earlier detection of low-grade dysplasia, a more frequent surveillance interval (1-2 years) would be appropriate. The US guidelines recommend a surveillance interval of 1 year following the confirmed finding of low-grade dysplasia. During this period 3.0% of these patients with low-grade dysplasia had progressed to high-grade dysplasia and 3.1% to adenocarcinoma. This incidence is lower than the 12.9%[95] and 12%[47] reported previously. Surveillance at 3 or 5 years would increase the proportion of patients developing high-grade dysplasia and adenocarcinoma to approximately 10%. Following the finding of high-grade dysplasia, 25% of patients had biopsies demonstrating adenocarcinoma within 0.1 years, and the median time to adenocarcinoma development was 0.6 years, comparable to some findings in the literature[97;276], but higher than those of others[90;277]. The results of this study support early aggressive treatment of high-grade dysplasia due to its extremely high malignant risk and improved outcome if resected early[278].

Significance of Finding of Intestinal Metaplasia in Non-Dysplastic Columnar-Lined Oesophagus

Histopathological opinion in the UK differs from the US concerning the relevance of the finding of intestinal metaplasia within the columnarised segment[91;121;256]. In 1997, only 12% of UK physicians undertaking surveillance based practice on the presence or absence of intestinal metaplasia[244], believing that if a sufficient number of biopsies are taken over a sufficient time period that intestinal metaplasia will always be detected[188]. Previous studies have demonstrated that the finding of intestinal metaplasia increases with patient age[247;248], cumulatively with number of surveillance endoscopies[249], increased length of gastro-oesophageal reflux symptoms[250], increased oesophageal exposure to bile[250] and macroscopic length of columnarised segment[249;251]. The finding of goblet cells is subject to sampling error[197;253-255] and is increased with the experience of the endoscopist[254] and number of biopsy samples taken from the metaplastic segment[256]. Additionally, patients who were first diagnosed with columnar-lined oesophagus without intestinal metaplasia have subsequently demonstrated intestinal metaplasia on further surveillance biopsies and later progressed to adenocarcinoma[87]. This study confirms each of these findings (with the exception of the increased finding of intestinal metaplasia with increasing age[247] and experience of the endoscopist[254]). Overall, 90% of patients who initially did not have

intestinal metaplasia on biopsy had intestinal metaplasia (or dysplasia/adenocarcinoma) detected within 10 years. This study did demonstrate that the finding of intestinal metaplasia was more common in males than females (table 6.RT23). The patients who initially had no intestinal metaplasia detected did not significantly differ from those with detected intestinal metaplasia in their rate of progression to dysplasia and adenocarcinoma (table 6.RT13). Consequently, this study would not support the presence or absence of intestinal metaplasia as a significant criterion on which surveillance practice is based.

Sources of Error in Interpretation of These Results

There are 3 major sources of potential error in this cohort. Firstly, the biopsy protocol (number, positioning and types of biopsy forceps used) and surveillance intervals were not controlled. The data were collected from 7 independent centres, broadly in a retrospective fashion. Consequently, there is a large potential for significant sampling error (with different biopsy protocols) and variability in time period of detection of histopathological changes. This is most obvious in the finding of intestinal metaplasia in non-dysplastic columnar-lined oesophagus and its increase with the number of samples of tissue examined by the histopathologist, and follow-up period. The high proportion of patients demonstrating high-grade dysplasia who had subsequent biopsies demonstrating adenocarcinoma within very short periods of time is also likely to be due to sampling error[184].

The second source of error is the interpretation of the tissue samples by the histopathologist. This is most variable in the middle part of the metaplasia-dysplasia-adenocarcinoma spectrum[95:189:281] and may account for the high proportion of patients with indefinite changes for dysplasia subsequently having low-grade dysplasia detected, but no increase in hazard of development of high-grade dysplasia or adenocarcinoma over non-dysplastic columnar-lined oesophagus. This variability in interpretation of dysplasia and adenocarcinoma may also be partially responsible for the high proportion of patients having adenocarcinoma detected early following the discovery of high-grade dysplasia in keeping with previous studies[189:281:282] and the median time to development of adenocarcinoma of 0.6 years is in keeping with the review of Pellegrini and Pohl, who stated that 43% of patients who underwent oesophagectomy for high-grade dysplasia harboured an occult

adenocarcinoma in the resected specimen[96]. Furthermore, there was no provision within the study for central verification of histopathology findings or comparison of interpretation of different histopathologists.

The final significant source of error is that of possible type II statistical error secondary to the relatively small number of patients in some groups, notably those with indefinite changes for dysplasia, high-grade dysplasia and adenocarcinoma. To avoid incorrect interpretation of survival analyses, results were not examined when 5 or fewer patients remained in the cohort, and projected results are not used. Consequently, if the study were continued for a longer period, or number of patients involved increased, the differences in the histological fate of the metaplastic segment over time would be likely to become more clearly defined.

Chapter 7 – Influence of Treatment on the Fate of the Metaplastic Segment

Aims and Introduction

Columnar Metaplasia of the Oesophagus and Gastro-Oesophageal Reflux Disease

Columnar metaplasia of the oesophagus is believed to be an acquired change, secondary to prolonged gastro-oesophageal reflux disease exposing the oesophagus to gastric and small intestinal contents. Its association with symptoms of gastro-oesophageal reflux disease, hiatal hernia and oesophageal inflammation had been demonstrated by the 1970s[81;149-151]. Animal models of gastro-oesophageal[52;53] and duodeno-oesophageal[55-58] reflux have resulted in columnar metaplasia of the oesophagus. The physiological mechanism for prevention of gastro-oesophageal reflux is control by the lower oesophageal sphincter, and this has been shown to be more defective in patients with columnar metaplasia of the oesophagus compared to patients with simple reflux oesophagitis or normal oesophageal mucosa[60]. Both the magnitude of acid[61] and biliary[62;63] reflux are greater in patients with columnar metaplasia of the oesophagus than in those with simple reflux oesophagitis and the combination of acid and biliary reflux is more strongly associated with the finding of columnar metaplasia than either alone[65]. Patients with the most extensive segments of columnar metaplasia have greater exposure to acid and bile than shorter segments, which (in turn) have greater exposure than patients with no segment of columnar metaplasia[66]. The duration of symptoms of gastro-oesophageal reflux[68], frequency of symptoms[68] and duration of individual reflux episodes[67] are greater in patients with columnar metaplasia than in patients with simple reflux oesophagitis.

Association between Gastro-Oesophageal Reflux Disease and Oesophageal Adenocarcinoma

A landmark Swedish population-based study by Lagergren *et al.*[39] demonstrated that prolonged symptoms of gastro-oesophageal reflux was the major risk factor for oesophageal adenocarcinoma, with an odds ratio of 7.8, rising to 43.5 in the patients with the longest and most severe symptoms of reflux. The magnitude of oesophageal reflux has

been shown to be higher in patients with high-grade dysplasia in metaplastic columnar-lined oesophagus than in non-dysplastic columnar-lined oesophagus[61].

Association between Columnar-Lined Oesophagus and Oesophageal Adenocarcinoma

The relative risk of adenocarcinoma development in patients with columnar-lined oesophagus has been estimated at 5-125x that of control populations[86;89;92;168;169]. Unfortunately oesophageal adenocarcinoma frequently presents late and is incurable at presentation[2;8;69].

Progression of Columnar-Lined Oesophagus to Oesophageal Adenocarcinoma

The adenocarcinoma risk is higher in patients with dysplasia, with an adenocarcinoma incidence of approximately 12% per annum in patients with low-grade dysplasia[47;95], and up to 67% per annum in patients with high-grade dysplasia[90;97;276;277]. The importance of dysplasia is further enforced as it is the basis upon which surveillance interval is determined by the American College of Gastroenterology Guidelines on the management of columnar-lined oesophagus[91]. The overall rate of progression to adenocarcinoma is 0.69% per annum (see appendix 1).

Influence of Duodeno-Gastro-Oesophageal Reflux on Development of Oesophageal Metaplasia and Adenocarcinoma

Animal models of reflux of duodenal contents into the oesophagus have induced oesophageal hyperproliferation and malignancy in rats[58;158-161;329-332]. However, reports in humans as to the relative importance of duodeno-gastro-oesophageal reflux are conflicting both in the development of oesophageal columnar metaplasia[62;165;166] and adenocarcinoma[25;89;164]. Gastric outlet surgery disrupts prevention of reflux of small intestinal contents into the stomach and subsequently into the oesophagus (in the presence of an incompetent gastro-oesophageal sphincter).

Management of Columnar-Lined Oesophagus

Goals of therapy in columnar-lined oesophagus include symptom control (where symptoms are present), healing of existing lesions, prevention of new non-neoplastic complications and minimisation of the risk of progression of adenocarcinoma. To this end, management is centred on two key areas – firstly: control of gastro-oesophageal reflux and secondly: surveillance for development of dysplasia and adenocarcinoma[91]. Gastro-oesophageal reflux may be controlled either medically by acid suppression therapy (principally currently proton pump inhibitors and previously by histamine H_2 receptor antagonists) or by antireflux surgery (principally fundoplication). As described above, patients with columnar-lined oesophagus are at the extreme end of the pathophysiological spectrum of gastro-oesophageal reflux disease[91] and, as a consequence of these factors, it is difficult to achieve normalisation of oesophageal acid and bile exposure in these patients. Proton pump inhibitors are effective in many patients in neutralising the pH of the acidic gastric contents and also reducing the volume of the refluxate; however, they do not protect the oesophagus from the reflux of bile and pancreatic secretions (as measured by bilitec)[65;126]. Several series have shown pathological acid exposure in up to 40% of columnar-lined oesophagus patients rendered symptom free on high dose proton pump inhibitor (Omeprazole 80mg daily)[124;129;130;153;154]. Oesophageal columnar metaplasia development has been demonstrated in gastro-oesophageal reflux patients whilst taking acid suppression therapy[127;128] and other series have suggested that antireflux surgery may protect against this metaplastic change[127;155-157]. Post-operative studies have shown that antireflux surgery is effective, both in controlling reflux symptoms[289] and on physiological testing of oesophageal acid and bile exposure[131-135]. Fundoplication would appear to have theoretical advantages over acid suppression therapy in patients with oesophageal columnar metaplasia as it is the only therapy which can eliminate hiatal hernia, correct lower oesophageal sphincter failure and consistently normalise both acid and duodenal juice exposure[283;288]. However, concerns remain that the long-term failure rate of surgical reflux control[133;138] may overcome the apparent early benefits. The American College of Gastroenterology states that "*as a group, patients with Barrett's have a greater esophageal acid exposure than other GERD patients, and control of symptoms may require higher than usual doses of proton pump inhibitors ... Patients who are appropriate surgical candidates may elect antireflux surgery*". Three small, uncontrolled series have suggested that fundoplication

confers a protective effect against adenocarcinoma[222;333;334] and two meta-analyses of published series which documented long term follow up and adenocarcinoma development came to opposite conclusions in this regard (table 7.IT1)[136;137].

Bammer *et al.*[136] reviewed the literature between 1977-99 and found 40 studies on columnar-lined oesophagus treatment and outcome. They found a trend for a lower adenocarcinoma incidence in patients treated surgically, and concluded that surgery was cost effective at 7 years compared to medical therapy (allowing for 20-40% of surgical patients continuing taking antireflux medication). They suggested that "*surgery may be superior to medical treatment to prevent progression of Barrett esophagus and the development of carcinoma*".

Corey *et al.*[137] reviewed 34 studies in the literature 1966-2001. Their results were similar to Bammer *et al.*[136], however, they concluded that "*surgical antireflux procedures do not seem to provide benefit over medical therapy in Barrett's esophagus in reducing the incidence of cancer development. Surgical antireflux procedures should not be recommended over medical therapy to decrease the cancer risk associated with Barrett's esophagus*".

Table 7.IT1 – Results of Meta-Analyses Comparing Medical to Surgical Therapy for Columnar-Lined Oesophagus

Study	Treatment	No. Studies	No. Pts	Total FU*	No. AC†	AC† Incidence
Bammer *et al.*[136]	Medical	21	669	2026.3	14	1/144.7
	Surgical	19	902	4121.7	14	1/294.4
Corey *et al.*[137]	Medical	24‡	918	4906.2	26	1/188.7¶
	Surgical	19‡	754	4678.3	18	1/259.9¶

* FU Follow-up [years]
† AC Adenocarcinoma
‡ 9 studies had both medical and surgical arms
¶ p=0.29

This study examines the difference in adenocarcinoma incidence between patients with oesophageal columnar metaplasia treated by medical and surgical therapies for gastro-oesophageal reflux disease and for any increased risk in the subpopulation who have undergone previous gastric outlet surgery.

Methods

This analysis was performed on patients who had been diagnosed with columnar-lined oesophagus at 7 centres throughout the UK, and whose previous surgical history and management of oesophageal reflux could be established. The patients were all registered with UKBOR, and were involved in an in-depth analysis on the natural history of columnar-lined oesophagus. Registry researchers visited the centres involved and extracted information from patients' hospital records – typically including endoscopy, histology and operation reports, correspondence following outpatient attendances and inpatient stays. The data were entered into a Microsoft Access database[321]. Patients from the 7 centres were included in the analyses of dysplasia and adenocarcinoma risk dependent on antireflux treatment and previous gastric outlet surgery if they fulfilled criteria which were based around the analyses performed.

Patient Selection

Patients were selected from the database for the analyses in this chapter if they fulfilled the following criteria:

1. Their medical history prior to the diagnosis of columnar-lined oesophagus could be established
2. If the patient had undergone antireflux surgery, the date of the surgery could be established
3. Patients had at least one histology report demonstrating columnar-lined oesophagus

For analysis of medical treatment of gastro-oesophageal reflux disease compared to surgical treatment and development of dysplasia and adenocarcinoma:

1. Medications which were taken following the diagnosis of columnar-lined oesophagus could be established at at least one point in time between this diagnosis date and prior to the most recent histology report

For analysis of risk of prevalent adenocarcinoma dependent on whether patients had previously undergone gastric outlet surgery:

1. Patients had at least one histopathological report demonstrating columnar-lined oesophagus

For analysis of the risk of dysplasia and oesophageal adenocarcinoma over time dependent on whether patients had previously undergone gastric outlet surgery:

1. Patients had at least one further biopsy from the metaplastic segment
2. Patients did not have the "target" histological changes (or changes of more dysplastic histology) at the diagnostic biopsy

The date of diagnosis was considered to be the first histological confirmation of columnar-lined oesophagus.

The overall rates of progression to the "target" histological changes of low-grade dysplasia, high-grade dysplasia and adenocarcinoma were examined using Kaplan-Meier survival analysis, and comparisons between groups were made using Cox's proportional hazards ratio analysis with covariates of gender, age at diagnosis, diagnostic histology (grouped as patients with columnar-lined oesophagus without intestinal metaplasia, columnar-lined oesophagus with intestinal metaplasia, changes indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia and adenocarcinoma[189]) and year of diagnosis. The analyses were first performed for different treatment groups (medical and surgical therapy). Secondly, the same analyses were performed comparing patients who had previously undergone gastric outlet surgery to those patients who had not (without examining what antireflux measures the patients had been treated with). The results were analysed for all patients (including both prevalent and incident events). Incidence data were modelled using an exact Poisson distribution.

- The follow-up period was defined as the period from the first histology report demonstrating the columnar-lined oesophagus, and terminated at the earliest biopsy demonstrating the low-grade dysplasia, high-grade dysplasia (or histology demonstrating more dysplastic features than this "target" histology), or (if this was not attained) the final histology report

- Patients were grouped into those treated with proton pump inhibitors, histamine H_2 receptor antagonists, both of these classes of drugs simultaneously, both of these classes of drugs sequentially, patients not taking either of these classes of drugs and patients who had undergone antireflux surgery
- If patients had undergone an intervention to the metaplastic segment, (oesophagectomy, endoscopic mucosal resection or ablation) then they were censored at the date of the histological report immediately preceding the intervention

Results

Influence of Anti-Reflux and Acid Suppression Treatment on Outcome of Columnar-Lined Oesophagus

Of the entire cohort, 864 patients fulfilled the criteria for the analyses. Of these, the total number of patients in each treatment group, number who developed low-grade dysplasia, number who developed high-grade dysplasia and number who developed adenocarcinoma are shown in table 7.RT1 and mean follow-up and gender breakdown are shown in table 7.RT2. The majority of patients diagnosed in the earliest part of the cohort were treated with no proton pump inhibitors or histamine H_2 receptor antagonists during the follow-up of their metaplastic columnar-lined oesophagus. Thereafter, histamine H_2 receptor antagonists became the treatment of choice, and patients treated solely by this class of medication were diagnosed with columnar-lined oesophagus at a mean average of 7 years earlier than those treated solely with proton pump inhibitors. Patients treated sequentially with histamine H_2 receptor antagonists and proton pump inhibitors were diagnosed on average between those treated solely with either class of drug and patients treated simultaneously with both of these classes of drugs were diagnosed (on average) at a similar time in the study period to those treated with proton pump inhibitors alone. The mean year of diagnosis of patients treated with antireflux surgery was a mean of 1.7 years earlier than patients treated solely with proton pump inhibitors and a mean of 5.6 years later than those treated solely with histamine H_2 receptor antagonists. To allow for any potential confounding effects of year of diagnosis, this was entered as a covariate into the survival analyses. There was no difference in the gender breakdown of the different treatment groups (table 7.RT2 Chi square 5 degrees of freedom $p=0.590$). There was significant variation in follow-up of the different treatment groups (ANOVA $p<0.001$), but this is allowed for in the survival analyses. Additionally, the mean age at diagnosis of columnar-lined oesophagus was lower in the patients who were treated with antireflux surgery by a mean of 8.9 years compared to those treated medically (independent t-test $p<0.001$), and amongst patients treated medically, there was variation in mean age at diagnosis between treatment groups (ANOVA $p=0.005$)(table 7.RT2).

Table 7.RT1 – Composition of the Treatment Analysis Cohort

Treatment Group	N (%)* Patients	N (%)† Developing LGD‡	N (%)† Developing HGD‡	N (%)† Developing AC‡
No H_2RA/PPI¶	18 (2.1%)	3 (16.7%)	0 (0%)	2 (11.1%)
H_2RA only¶	59 (6.8%)	9 (15.3%)	0 (0%)	8 (13.6%)
PPI only¶	620 (71.8%)	128 (20.6%)	21 (3.4%)	22 (3.5%)
H_2RA and PPI sequentially¶	99 (11.5%)	26 (26.3%)	0 (0%)	3 (3.0%)
H_2RA and PPI simultaneously¶	20 (2.3%)	7 (35.0%)	0 (0%)	1 (5.0%)
Antireflux Surgery¶	48 (5.6%)	6 (12.5%)	0 (0%)	2 (4.2%)

* Percentage of entire cohort
† Percentage of treatment group
‡ LGD Low-grade dysplasia
‡ HGD High-grade dysplasia
‡ AC Adenocarcinoma
¶ PPI Proton pump inhibitor
¶ H_2RA Histamine H_2 receptor antagonist

Table 7.RT2 – Gender Breakdown, Age at Diagnosis and Follow-Up of Different Treatment Groups

Treatment Group	% Male	Mean Age at Diagnosis [years]	Mean FU† [Years]
No H_2RA/PPI*	66.7%	68.9	1.7
H_2RA only*	61.0%	65.1	4.0
PPI only*	68.4%	60.5	3.9
H_2RA and PPI sequentially*	67.7%	60.1	7.1
H_2RA and PPI simultaneously*	60.0%	60.7	4.9
Antireflux Surgery	68.8%	52.1	5.4

* PPI Proton pump inhibitor
* H_2RA Histamine H_2 receptor antagonist
† FU Follow-up

The number of patients and annual incidence of low-grade dysplasia, high-grade dysplasia and adenocarcinoma dependent on treatment group is shown in table 7.RT3-7.RT5 for all patients and in table 7.RT6-7.RT8 for patients with at least 1 year of follow-up.

Table 7.RT3 – Annual Incidence of Progression to Low-Grade Dysplasia, High-Grade Dysplasia or Adenocarcinoma Dependent on Treatment Group for All Patients

Treatment Group	Annual Incidence	95% CI* for Annual Incidence
No H_2RA/PPI†	17.0%	5.5-39.7%
H_2RA only†	7.7%	4.5-12.4%
PPI only†	8.5%	7.3-9.9%
H_2RA and PPI sequentially†	4.9%	3.3-7.1%
H_2RA and PPI simultaneously†	9.6%	4.1-18.9%
Antireflux Surgery	3.3%	1.4-6.5%

* CI Confidence Interval for exact Poisson distribution
† PPI Proton pump inhibitor
† H_2RA Histamine H_2 receptor antagonist

Table 7.RT4 – Annual Incidence of High-Grade Dysplasia or Adenocarcinoma Dependent on Treatment Group for All Patients

Treatment Group	Annual Incidence	95% CI* for Annual Incidence
No H_2RA/PPI†	6.7%	0.0-24.3%
H_2RA only†	3.4%	1.5-6.6%
PPI only†	1.7%	1.3-2.4%
H_2RA and PPI sequentially†	0.4%	0.1-1.2%
H_2RA and PPI simultaneously†	1.0%	-
Antireflux Surgery	0.8%	0.0-2.8%

* CI Confidence Interval for exact Poisson distribution
† PPI Proton pump inhibitor
† H_2RA Histamine H_2 receptor antagonist

Table 7.RT5 – Annual Incidence of Adenocarcinoma Dependent on Treatment Group for All Patients

Treatment Group	Annual Incidence	95% CI* for Annual Incidence
No H_2RA/PPI†	6.7%	0.0-24.2%
H_2RA only†	3.4%	1.5-6.6%
PPI only†	0.9%	0.6-1.4%
H_2RA and PPI sequentially†	0.4%	0.1-1.2%
H_2RA and PPI simultaneously†	1.0%	-
Antireflux Surgery	0.8%	0-2.8%

* CI Confidence Interval for exact Poisson distribution
† PPI Proton pump inhibitor
† H_2RA Histamine H_2 receptor antagonist

Table 7.RT6 – Annual Incidence of Low-Grade Dysplasia, High-Grade Dysplasia and Adenocarcinoma Dependent on Treatment Group for Patients Followed-Up for At Least One Year

Treatment Group	Annual Incidence	95% CI* for Annual Incidence
No H_2RA/PPI†	3.7%	-
H_2RA only†	3.3%	1.3-6.7%
PPI only†	3.8%	3.0-4.8%
H_2RA and PPI sequentially†	2.9%	1.7-4.7%
H_2RA and PPI simultaneously†	8.4%	3.4-17.3%
Antireflux Surgery	1.7%	0.5-4.0%

* CI Confidence Interval for exact Poisson distribution
† PPI Proton pump inhibitor
† H_2RA Histamine H_2 receptor antagonist

Table 7.RT7 – Annual Incidence of High-Grade Dysplasia or Adenocarcinoma Dependent on Treatment Group for Patients Followed-Up for At Least One Year

Treatment Group	Annual Incidence	95% CI* for Annual Incidence
No H_2RA/PPI†	0.0%	-
H_2RA only†	1.7%	0.5-4.4%
PPI only†	1.0%	0.6-1.5%
H_2RA and PPI sequentially†	0.4%	0.1-1.2%
H_2RA and PPI simultaneously†	0.0%	-
Antireflux Surgery	0.0%	-

* CI Confidence Interval for exact Poisson distribution
† PPI Proton pump inhibitor
† H_2RA Histamine H_2 receptor antagonist

Table 7.RT8 – Annual Incidence of Adenocarcinoma Dependent on Treatment Group for Patients Followed-Up for At Least One Year

Treatment Group	Annual Incidence	95% CI* for Annual Incidence
No H_2RA/PPI†	0.0%	-
H_2RA only†	1.7%	0.5-4.4%
PPI only†	0.5%	0.2-0.9%
H_2RA and PPI sequentially†	0.4%	0.1-1.2%
H_2RA and PPI simultaneously†	0.0%	-
Antireflux Surgery	0.0%	-

* CI Confidence Interval for exact Poisson distribution
† PPI Proton pump inhibitor
† H_2RA Histamine H_2 receptor antagonist

Comparison of Different Treatment Groups and Dysplasia and Adenocarcinoma Development

The number of patients (and events) in the no proton pump inhibitor or histamine H_2 receptor antagonist group was too small to allow a meaningful survival analysis. The group of patients treated with both of these classes of drugs together was also small, and so this group was combined with the group of patients treated with proton pump inhibitors only. Subsequently the four treatment groups analysed in the survival analyses for development

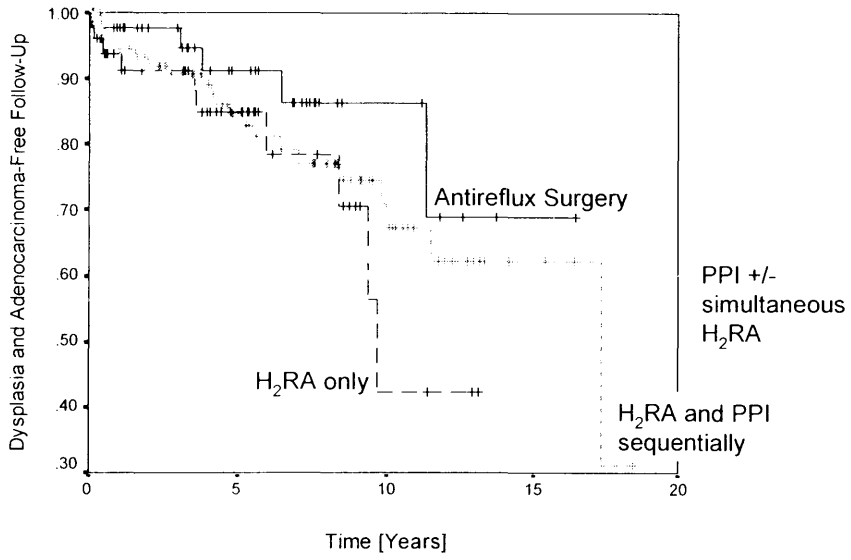
of low-grade dysplasia, high-grade dysplasia and adenocarcinoma were: histamine H_2 receptor antagonists only, histamine H_2 receptor antagonists and proton pump inhibitors sequentially, proton pump inhibitors (with or without simultaneous histamine H_2 receptor antagonists) and antireflux surgery. Cox's proportional hazards ratios were performed examining the difference in risk of development of the target histology groups (stated above) dependent on treatment group with the covariates of gender, age at diagnosis of columnar-lined oesophagus, year of diagnosis and diagnostic histology.

The proportional hazards ratios for the development of dysplasia or adenocarcinoma examined pair-wise are shown in table 7.RT9, and the survival graph is shown in figure 7.RF1. There were no significant differences in hazard of low-grade dysplasia development between any of the pairs of treatment groups, but a tendency towards antireflux surgery in being protective over all medical treatments, with an overall hazards ratio of 1.892 comparing all medical groups to antireflux surgery.

Table 7.RT9 – Hazards Ratios for Low-Grade Dysplasia, High-Grade Dysplasia and Adenocarcinoma Development between Treatment Groups

Treatment Groups*	p Value	Hazards Ratio	95% CI† for Hazards Ratio
PPI+/-simultaneous H_2RA vs. Antireflux Surgery	0.202	1.821	0.725-4.576
H_2RA and PPI sequentially vs. Antireflux Surgery	0.777	1.181	0.374-3.731
H_2RA only vs. Antireflux Surgery	0.988	1.012	0.200-5.117
H_2RA and PPI sequentially vs. PPI+/-simultaneous H_2RA	0.396	0.799	0.476-1.342
H_2RA only vs. PPI+/-simultaneous H_2RA	0.856	0.936	0.458-1.912
H_2RA only vs. H_2RA and PPI sequentially	0.345	1.466	0.663-3.240
All Medical Therapy vs. Antireflux Surgery	0.212	1.892	0.694-5.157

Figure 7.RF1 Development of Dysplasia and Adenocarcinoma Dependent on Treatment Group



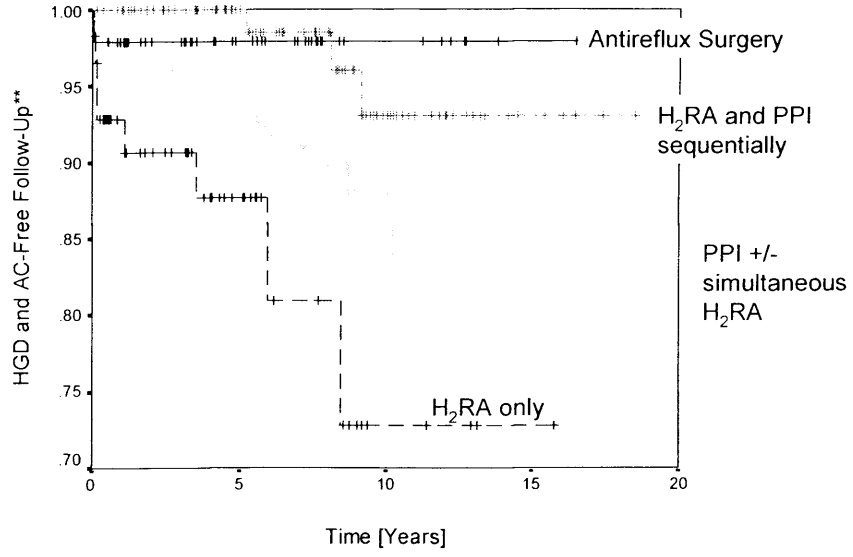
* PPI Proton pump inhibitor
* H_2RA Histamine H_2 receptor antagonist
† CI Confidence interval

Examination for development of high-grade dysplasia and adenocarcinoma (but not low-grade dysplasia) produced much wider confidence intervals due to the smaller number of patients developing these target histology groups. There was a tendency for a higher hazard associated with treatment with a histamine H_2 receptor antagonist compared to proton pump inhibitor (with or without simultaneous histamine H_2 receptor antagonist); and a statistically higher hazard for patients treated with a histamine H_2 receptor antagonist compared to patients treated sequentially with histamine H_2 receptor antagonist and proton pump inhibitors (hazards ratio 16.253). There was a less strong trend for antireflux surgery over all medical therapies grouped together compared to the end-point of all dysplasia and adenocarcinoma. These results are shown in table 7.RT10 and figure 7.RF2).

Table 7.RT10 – Hazards Ratios for High-Grade Dysplasia and Adenocarcinoma Development between Treatment Groups

Treatment Groups*	p Value	Hazards Ratio	95% CI† for Hazards Ratio
PPI+/-simultaneous H_2RA vs. Antireflux Surgery	0.387	2.428	0.325-18.137
H_2RA and PPI sequentially vs. Antireflux Surgery	0.228	0.066	0.001-5.455
H_2RA only vs. Antireflux Surgery	0.606	1.999	0.144-27.698
H_2RA and PPI sequentially vs. PPI+/-simultaneous H_2RA	0.056	0.300	0.087-1.032
H_2RA only vs. PPI+/-simultaneous H_2RA	0.083	2.285	0.898-5.812
H_2RA only vs. H_2RA and PPI sequentially	0.002	16.253	2.673-98.829
All Medical Therapy vs. Antireflux Surgery	0.669	1.585	0.192-13.106

Figure 7.RF2 Development of High-Grade Dysplasia and Adenocarcinoma Dependent on Treatment Group



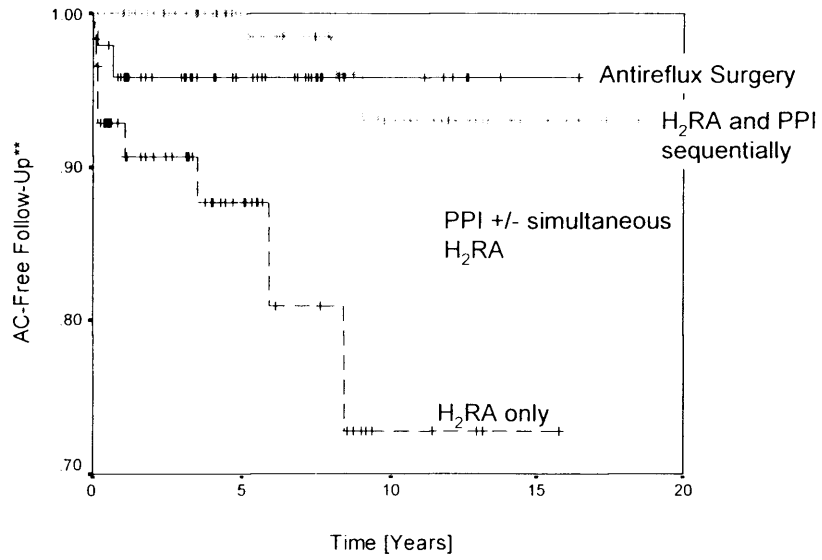
* PPI Proton pump inhibitor
* H_2RA Histamine H_2 receptor antagonist
† CI Confidence interval
** HGD High-grade dysplasia
** AC Adenocarcinoma

The only patients who had the detection of high-grade dysplasia without subsequent adenocarcinoma development during the course of follow-up were in the proton pump inhibitors with or without simultaneous histamine H_2 receptor antagonists group. Consequently, for the most part, the results for all other pairs are similar to the analyses for the hazard of high-grade dysplasia and adenocarcinoma development (table 7.RT10 and figure 7.RF2). The hazard of adenocarcinoma development was significantly higher in patients treated with histamine H_2 receptor antagonist only over proton pump inhibitors (with or without simultaneous histamine H_2 receptor antagonists) with a hazards ratio of 2.952 and proton pump inhibitors and histamine H_2 receptor antagonists sequentially with a hazards ratio of 16.253. Unlike the development of either dysplasia or adenocarcinoma, there was a trend for patients treated with antireflux surgery to have a higher hazard of adenocarcinoma development when compared to all medical treatments grouped together.

Table 7.RT11 – Hazards Ratios for Adenocarcinoma Development between Treatment Groups

Treatment Groups*	p Value	Hazards Ratio	95% CI† for Hazards Ratio
PPI+/-simultaneous H_2RA vs. Antireflux Surgery	0.967	0.967	0.201-4.654
H_2RA and PPI sequentially vs. Antireflux Surgery	0.159	0.046	0.001-3.317
H_2RA only vs. Antireflux Surgery	0.657	1.822	0.129-25.782
H_2RA and PPI sequentially vs. PPI+/-simultaneous H_2RA	0.248	0.465	0.127-1.706
H_2RA only vs. PPI+/-simultaneous H_2RA	0.045	2.952	1.026-8.489
H_2RA only vs. H_2RA and PPI sequentially	0.002	16.253	2.673-98.829
All Medical Therapy vs. Antireflux Surgery	0.368	0.450	0.079-2.559

Figure 7.RF3 Development of Adenocarcinoma Dependent on Treatment Group



* PPI Proton pump inhibitor
* H_2RA Histamine H_2 receptor antagonist
† CI Confidence interval
** AC Adenocarcinoma

Influence of Gastric Outlet Surgery on the Development of Dysplasia and Adenocarcinoma

Of the entire cohort of 2011 patients with biopsy-proven columnar-lined oesophagus, 51 had undergone gastric outlet surgery (typically for peptic ulcer disease) prior to their diagnoses of columnar-lined oesophagus. Patients who had undergone previous gastric outlet surgery did not differ significantly from the remainder of the cohort with regards to gender (Chi square 1 degree of freedom p=0.769), diagnostic histology (Chi square 5 degrees of freedom p=0.194) and age at columnar-lined oesophagus diagnosis (independent t-test p=0.355). However, patients who had previously undergone gastric outlet surgery were diagnosed at an average of 3.1 years earlier in the cohort (when examining year of diagnosis) compared to those who had not (independent t-test p<0.001). The proportion of patients who developed prevalent adenocarcinoma was identical in the patients who had previously undergone gastric outlet surgery to those who had not (5.9% of patients who had undergone previous gastric outlet surgery and 5.8% of the remainder of the cohort, Chi

square 1 degree of freedom p=0.573). The development of low-grade dysplasia, high-grade dysplasia and adenocarcinoma over time were examined using survival analyses and comparisons between patients who had previously undergone gastric outlet surgery and the remainder of the cohort was examined using Cox's proportional hazards ratio with the covariates of age at columnar-lined oesophagus diagnosis, gender, year of diagnosis and diagnostic histology in addition to the dichotomous variable of previous gastric outlet surgery or not. The number and proportion of patients developing dysplasia and adenocarcinoma who had undergone previous gastric outlet surgery and those who had not are shown in table 7.RT12. There was a tendency for a greater proportion of patients who had previously undergone gastric outlet surgery to develop the changes of dysplasia and adenocarcinoma, but there was no statistically significant difference in the hazard of development of these changes (table 7.RT13).

Table 7.RT12 – Proportion of Patients Developing Dysplasia and Adenocarcinoma Dependent on Presence of Absence of Previous Gastric Outlet Surgery

End-Point Histology*	N (%†) Previous Gastric Outlet Surgery	N (%†) No Previous Gastric Outlet Surgery
Low-Grade Dysplasia	12/31 (38.7%)	164/838 (19.6%)
High-Grade Dysplasia	5/32 (15.6%)	57/936 (6.1%)
Adenocarcinoma	4/32 (12.5%)	48/951 (5.0%)

* Or more dysplastic changes
† Percent of surgery/non-surgery group

Table 7.RT13 – Hazard of Development of Dysplasia and Adenocarcinoma Dependent on Whether Patients had Previously Undergone Gastric Outlet Surgery

End-Point Histology*	p Value	Hazards Ratio	95% CI† for Hazards Ratio
Low-Grade Dysplasia	0.256	1.414	0.778-2.569
High-Grade Dysplasia	0.180	1.895	0.744-4.825
Adenocarcinoma	0.276	1.786	0.628-5.075

* Or more dysplastic changes
† CI Confidence interval

The annual incidence of all dysplasia and adenocarcinoma in the gastric outlet surgery group was 6.7% (95% confidence interval for exact Poisson distribution 3.5-11.7%) and in the non-gastric outlet surgery group was 5.1% (95% confidence interval 4.3-5.9%),

producing a hazards ratio of 1.414 (p=0.256). The annual incidence of high-grade dysplasia and adenocarcinoma in the gastric outlet surgery group was 2.6% (95% confidence interval 0.8-6.1%) and in the non-gastric outlet surgery group was 1.5% (95% confidence interval 1.1-1.9%), producing a hazards ratio of 1.895 (p=0.180). The annual incidence of adenocarcinoma in the gastric outlet surgery group was 2.0% (95% confidence interval 0.5-5.1%) and in the non-gastric outlet surgery group was 1.3% (95% confidence interval 0.9-1.7%), producing a hazards ratio of 1.786 (p=0.276).

Discussion and Conclusions

Treatment of Columnar-Lined Oesophagus

The goal of treatment of columnar-lined oesophagus is to prevent non-neoplastic complications and development of dysplasia and adenocarcinoma by control of gastro-oesophageal reflux[91]. The escalating incidences of columnar-lined oesophagus[72-76;207] and adenocarcinoma[4-6;8;9;11-14;22;27;174;175] have significant implications for the cost of surveillance[117-120], treatment of gastro-oesophageal reflux[119;120] and treatment of neoplastic complications[117;119;120]. These patients with columnar-lined oesophagus are amongst those with the most severe gastro-oesophageal reflux disease[59-61;66-68] and adequate control of reflux is difficult, with a number of patients still having acid reflux (frequently asymptomatically[152]) when on high-dose acid suppression medication[124;153;154]. Medical therapy does not prevent biliary reflux into the oesophagus[65;126], and only surgical (mechanical) correction of the defective gastro-oesophageal sphincter can abolish this[135;260]. The findings of columnar-lined oesophagus developing in patients with gastro-oesophageal reflux disease whilst taking antireflux medication[127;128] and development of adenocarcinoma in these patients clearly call for more aggressive measures of prevention of carcinogenic reflux. Whilst surgery is effective in the short-term at preventing reflux, the long-term failure rate[133;138] may overcome the early benefits; and these patients may subsequently require "re-do" surgery or concomitant medical therapy. This cohort showed that the treatment trends over time had altered with regard to medical therapy, with the proton pump inhibitors only being employed in the latter part of the cohort, and antireflux surgery being used throughout the cohort.

Efficacy of Medical Treatment Compared to Surgical Treatment

This cohort included patients with and without intestinal metaplasia on biopsy as these patients have been shown in previous studies to have a risk of adenocarcinoma development[87] and this was also shown in chapters 5 and 6. The hazards analyses have controlled for any confounding effects of gender, age at columnar-lined oesophagus diagnosis, year at diagnosis and diagnostic histology. However, it should be noted that the patients treated with antireflux surgery were younger than those treated medically by a

mean average of 7.5 years and although their malignant risk at this age is lower than that of older patients (see chapter 4), they are also the patients who have the longest period of gastro-oesophageal reflux ahead of them. The groups of patients treated with no histamine H_2 receptor antagonist or proton pump inhibitor and histamine H_2 receptor antagonist and proton pump inhibitor simultaneously were both small, so consequently evaluation of proportional hazard in these groups alone was not appropriate.

The overall hazard ratio comparing all medical to surgical therapy for the development of all dysplasia and adenocarcinoma was 1.892 (table 7.RT9 and figure 7.RF1), for development of high-grade dysplasia and adenocarcinoma was 1.585 (table 7.RT10 and figure 7.RF2) and for development of adenocarcinoma alone was 0.450 (table 7.RT11 and figure 7.RF3). These results did not reach statistical significance. There were statistically higher risks of development of high-grade dysplasia and adenocarcinoma or adenocarcinoma alone in the histamine H_2 receptor antagonist group compared to the group of patients treated with histamine H_2 receptor antagonists followed by proton pump inhibitors. This latter group had a very low hazard of either high-grade dysplasia or adenocarcinoma development. The major difference between the hazards ratios calculated between the development of high-grade dysplasia and adenocarcinoma and adenocarcinoma only was due to the 21 patients in the proton pump inhibitor (with or without histamine H_2 receptor antagonist) group who developed high-grade dysplasia. Many of the patients treated medically who developed high-grade dysplasia underwent an intervention such as photodynamic therapy at this point (accounting for the difference between the outcome measures of high-grade dysplasia or adenocarcinoma and adenocarcinoma alone). The exclusion of patients followed-up for less than one year (and prevalent cases) indicated a trend for lower risks for dysplasia and adenocarcinoma in the antireflux surgery group (where both cases of adenocarcinoma were prevalent cases) compared to the medical therapy groups (where the events occurred throughout the follow-up periods)(tables 7.RT6-7.RT8), but the small number of events produced wide confidence limits (which with no events in one group would not allow a proportional hazards analysis). Nonetheless, no cases of incident adenocarcinoma occurred in the antireflux surgery group, and using the surrogate outcome measure of all dysplasia and adenocarcinoma (table 7.RT9 and figure 7.RF1) demonstrated a trend for lower rates of all dysplasia in the surgical group (hazards ratio 1.892, $p=0.212$) after correction for the confounding factors. This still

suggests a possible superior protective effect of antireflux surgery compared to patients treated with all medical therapies.

The groups were not controlled for the severity of reflux at commencement of treatment as measured by oesophageal physiological studies and once treatment was commenced, there was no control to ensure that patients had adequate reflux control. Furthermore, there was no examination of whether patients treated surgically were also medicating with over-the-counter antacids or prescribed antireflux medications (62% in one large series of gastro-oesophageal reflux disease[225]). Approximately one half of the patients who underwent antireflux surgery did so before the diagnosis of columnar-lined oesophagus was made, and one half after this diagnosis. This may have been due to failure of endoscopists to recognise the metaplastic segment prior to antireflux surgery or its development following surgery. Clearly this study cannot support the hypothesis that antireflux surgery reliably prevents the development of oesophageal columnar metaplasia.

The results of this study are similar to both of the 2 meta-analyses[136;137]. The adenocarcinoma incidence reported by Bammer *et al.*[136] for patients treated medically was 0.7% per annum (95% confidence limits for exact Poisson distribution calculated at 0.2% and 1.2%) and for surgical therapy was 0.3% per annum (95% confidence limits calculated at 0.2% and 0.6%). Corey *et al.*[137] reported an annual adenocarcinoma incidence in patients treated medically at 0.5% (95% confidence limits calculated at 0.3% and 0.8%) and for patients treated surgically 0.4% per annum (95% confidence limits calculated at 0.2% and 0.6%). This study found the annual incidence of adenocarcinoma (including prevalent adenocarcinoma) was 0.8% (exact Poisson distribution 95% confidence interval 0.0 to 2.8%) in patients treated surgically and 1.0% (95% confidence interval 0.7% to 1.4%) in patients treated medically or, if prevalent cancers were excluded, 0.0% in patients treated surgically and 0.6% (95% confidence interval 0.4 to 0.9%) in those treated medically.

Influence of Gastric Outlet Surgery

Animal models have shown that surgical induction of reflux of duodenal contents into the oesophagus results in oesophageal hyperproliferation and malignancy[58;158-161;329-332]. The reports of previous studies of humans who have undergone gastric outlet surgery have been conflicting in its role in the pathogenesis of oesophageal adenocarcinoma development[25;89;164]. The results of this study suggest a tendency for patients with

columnar-lined oesophagus who had previously undergone gastric outlet surgery to be at a higher risk of development of dysplasia within the metaplastic segment and of adenocarcinoma development compared to the remainder of the cohort, with a hazards ratio 1.414 for the development of all dysplasia and adenocarcinoma, 1.895 for the development of high-grade dysplasia and adenocarcinoma and 1.786 for the development of adenocarcinoma alone. Examining for risk of prevalent adenocarcinoma development alone did not demonstrate any increased risk in the gastric outlet surgery group. The mean time from the gastric outlet surgery to the diagnosis of oesophageal columnar metaplasia was 15 years, and these patients were also diagnosed on average earlier in the cohort than the patients who had not undergone gastric outlet surgery reflecting the change in management for peptic ulcer disease from surgery to *helicobacter pylori* eradication.

Sources of Error

This study was purely observational, with no influence upon individual centres or clinicians' management as far as either treatment or surveillance practice. Consequently there was no randomisation or control of either the timing or type of treatment. Specific medication prescribed, dosing, frequency and compliance of patients treated medically were not examined, neither was type of antireflux or gastric outlet surgery and the approach (transabdominal, transthoracic, thoracoabdominal or laparoscopic) to the procedures.
Bias for treatment in patients with what is perceived to be the most severe disease and highest cancer risk[59-61;66-68] may have caused these patients to be treated with specific therapies – which could not be controlled for in the analyses. Patients were grouped by lists of prescribed medications on any date within the follow-up period, which (with the exception of the sequential treatment group) did not ensure continuous treatment or allow for variations in dosage. The study also could not evaluate prescription information held only by the patients' general practitioners.
Due to the low risk of high-grade dysplasia and adenocarcinoma, the power of this study to detect differences was limited, and subject to significant type II statistical error especially in the comparison of antireflux surgery to medical patients and in the comparison of patients who had undergone previous gastric outlet surgery to the remainder of the cohort. The small number of events (development of dysplasia or adenocarcinoma) produced the wide confidence intervals evaluated in the incidence analyses. Due to the nature of the

Poisson distribution, it is not possible to evaluate a confidence interval for groups in which there were one or no events. Short follow-up (especially in the no histamine H_2 receptor antagonist or proton pump inhibitor group) also contributed to the small number of patients developing dysplasia or adenocarcinoma and potential for error in this analysis. The shorter follow-up of the group treated with no histamine H_2 receptor antagonists or proton pump inhibitors also narrowed the window during which a medication report could be found in this group. This may also have had a confounding effect on this group which showed a trend to have a higher hazard of development of dysplasia or adenocarcinoma. Only patients with histological follow-up were included in the analyses. This may overestimate the risk of adenocarcinoma development as it excludes patients undergoing follow-up who were not biopsied (see chapter 4). Clinicians may also have elected only to follow-up those patients who they perceived to be at greatest risk of dysplasia or carcinoma development (such as those with the longest metaplastic segments or dysplasia – see chapter 5), or excluded other patients who would not be candidates for oesophageal resection[91] (see chapter 9).

The centres practised independently, determining their own frequency of surveillance endoscopy, biopsy protocol and verification of histopathological reporting. This will have allowed variations in sampling error and interobserver variability in histopathological interpretation of biopsy samples. However, the large number of patients involved and pooling of data between centres will have reduced each of these effects.

Chapter 8 – The Influence of Symptom Type and Duration on the Fate of the Metaplastic Segment

Introduction

Long-Standing Gastro-Oesophageal Reflux and Oesophageal Adenocarcinoma

For over 30 years, the association between long-standing gastro-oesophageal reflux disease and oesophageal adenocarcinoma has been known[42-44]. The strongest evidence for this association is from a large Swedish population-based study[39] which reported an odds ratio for the most frequent symptoms (3x per week compared to no reflux symptoms) of 16.7, for the most severe symptoms (compared to no reflux symptoms) of 20.0 and for the longest duration of symptoms (more than 20 years) of 16.4. The presence of night symptoms was associated with a risk ratio of nearly 11, and overall, patients with the longest duration, most severe and frequent symptoms had an odds ratio of 43.5. The most frequently observed symptom of the adenocarcinoma itself is dysphagia, which occurs in 70% or more of patients[69;221;291;292], 40% have symptoms of weight loss at diagnosis[292] and smaller proportions present with upper gastrointestinal bleeding or anaemia[221;292], nausea/vomiting[292] and chest pain[221]. Animal models of gastro-oesophageal reflux and duodeno-oesophageal reflux have also demonstrated this neoplastic risk[58;158-160].

Gastro-Oesophageal Reflux Disease and Columnar Metaplasia

The pre-malignant change in the development of oesophageal adenocarcinoma is that of columnar metaplasia. Evidence for this originated from studies of resected specimens showing metaplastic columnar epithelium surrounding the tumour, frequently with areas of dysplasia[22;29;44-51] and animal models of gastro-oesophageal reflux and duodeno-oesophageal reflux have induced columnar metaplasia of the oesophagus[52-58]. The severity of oesophageal acid reflux[59;61;63] and biliary reflux[62;63] have been shown to be higher in patients with columnar metaplasia over those with simple reflux oesophagitis or non-erosive reflux disease, and the combination of acid and biliary reflux induced columnar metaplasia more frequently than either alone[64;65]. These patients with columnar metaplasia also have the most defective anti-reflux mechanisms[60].

Progression of Columnar-Lined Oesophagus to Oesophageal Adenocarcinoma

The overall progression rate of columnar-lined oesophagus is 0.69% per annum (see appendix 1). The rate in patients with prior dysplasia is higher than in non-dysplastic columnar-lined oesophagus[47;90;95;96;277].

Treatment of Gastro-Oesophageal Reflux Disease and Columnar-Lined Oesophagus

The American College of Gastroenterology guidelines state that the goals of therapy of patients with columnar-lined oesophagus are the same as for gastro-oesophageal reflux disease: control of symptoms and the maintenance of a healed mucosa. To this end, the management is centred on the elimination of gastro-oesophageal reflux by medical or surgical therapy. However these therapies do not prevent the development of columnar-lined oesophagus in patients with gastro-oesophageal reflux disease[127;128] or development of dysplasia or adenocarcinoma[136;137].

Symptoms and Progression to Adenocarcinoma

A US householder survey demonstrated that the proportion of the general population suffering symptoms of gastro-oesophageal reflux was 29%[206], but only the minority of these patients develop oesophageal columnar metaplasia[59;77;79-83;150] and those who have developed oesophageal columnar metaplasia have a longer duration of symptoms than those with simple reflux oesophagitis[67]. Patients with intestinal metaplasia have a longer duration of symptoms than those without goblet cells in their biopsy specimens[250] and it is the patients with the longest duration of reflux symptoms who have been shown to be those at greatest risk of adenocarcinoma[39]. The frequency of symptoms has also been shown to be higher in patients with oesophageal columnar metaplasia than patients with reflux oesophagitis in some studies[154;224;227;248], but this difference has not been demonstrated by all studies[67]. More frequent symptoms of reflux have also been correlated with a higher risk of adenocarcinoma[39] and in some studies development of intestinal metaplasia, dysplasia and adenocarcinoma occurred most frequently in patients with persistent symptoms despite antireflux therapy[186;289].

Most patients with columnar-lined oesophagus present with heartburn and acid regurgitation[82;203;221;222;224], but some present with dysphagia (often secondary to a benign oesophageal stricture)[82;203;221;289], upper gastrointestinal bleeding or anaemia[203;221;222] and various other gastrointestinal or general symptoms[203;222]. The presence of nocturnal reflux symptoms has not been correlated with the development of oesophageal columnar metaplasia[224], but was associated with the development of adenocarcinoma with an odds ratio of nearly 11[39]. Dysphagia is the over-riding symptom of oesophageal adenocarcinoma[69;221;291;292], but reflux[186;187], weight loss[69;291;292], upper gastrointestinal bleeding or anaemia[69;291;292], chest pain[221], nausea/vomiting[292] and dyspepsia[222] have also been correlated with the development of dysplasia and adenocarcinoma. The presence of persistent symptoms of reflux in these patients has been correlated with physiological findings of pathological acid and bile reflux[186].

However, not all patients with columnar lined oesophagus are symptomatic, and up to 19% have no upper gastrointestinal symptoms at diagnosis[82;221;290]. A screening study demonstrated columnar-lined oesophagus in 24% of asymptomatic subjects[78] and an autopsy study suggested a prevalence of 1 in 76 of the population of Ormsted County, Minnesota[72]. Furthermore, up to 40% of patients with columnar-lined oesophagus who are rendered symptom-free on up to 80mg daily of Omeprazole still have pathological acid exposure[124;129;130].

Methods

This analysis was performed on patients who had been diagnosed with columnar-lined oesophagus at 7 centres throughout the UK, and whose presenting symptom type or duration could be established. The patients were all registered with UKBOR, and were involved in an in-depth analysis on the natural history of columnar-lined oesophagus. Registry researchers visited the centres involved and extracted information from patients' hospital records – typically including endoscopy, histology and operation reports, correspondence following outpatient attendances and inpatient stays. The data were entered into a Microsoft Access database[321]. Patients from the 7 centres were included in the analyses of development of columnar metaplasia, intestinal metaplasia, dysplasia and adenocarcinoma if information was available concerning their date of onset and types of symptoms if they fulfilled criteria, which were based around the analyses performed.

Patient Selection

Patients were selected from the database for the analyses in this chapter if they fulfilled the following criterion:

1. They had a biopsy demonstrating columnar-lined oesophagus

For analysis of length of symptom history:

1. A date of symptom onset preceding the diagnosis of columnar-lined oesophagus

For analysis of symptom type and dysplasia risk:

1. Presence of at least one type of symptom prior to diagnosis of columnar-lined oesophagus

The date of diagnosis was considered to be the first histological confirmation of columnar-lined oesophagus.

Different types of symptoms were classified into 7 categories shown in table 8.MT1.

Table 8.MT1 – Groups of Symptom Types

Symptom Group	Symptoms Incorporated into Group
Heartburn	Heartburn Reflux/Regurgitation
Abdominal Pain	Epigastric pain Other abdominal pain
Vomiting etc.	Nausea Vomiting Belching
Swallowing	Dysphagia Odynophagia
Bleeding	Upper gastrointestinal haemorrhage Anaemia
Weight loss	Weight loss
Night-time symptoms	Presence of any of the above at night

The data were explored for discrepancies between symptom types and age at diagnosis, gender and follow-up time. Differences between proportions of categorical variables were examined using Pearson χ^2 and between continuous variables using independent t-test. Differences in these variables (age, gender and year of diagnosis) were controlled for by entering these variables as covariates into the analyses below.

For the analysis of symptom type and dysplasia and adenocarcinoma risk, a binary logistic regression was performed with the covariates of gender, age at diagnosis, year of diagnosis and each of the seven symptom categories in the table (8.MT1). The regression was undertaken 3 times, with 3 different outcome measures: development of all dysplasia and adenocarcinoma, development of high-grade dysplasia and adenocarcinoma and development of adenocarcinoma alone.

For the analysis of the association between duration of symptoms, the time from the onset of all upper gastro-intestinal symptoms to the "target" histological findings of columnar-lined oesophagus without intestinal metaplasia, columnar-lined oesophagus with intestinal metaplasia, indefinite changes for dysplasia, low-grade dysplasia, high-grade dysplasia and adenocarcinoma were examined using Kaplan-Meier survival analysis. Differences in duration of symptoms to the diagnosis of columnar-lined oesophagus were examined between the diagnostic histology groups using one-way analysis of variance. Patients were

censored at their first demonstration of the "target" histology or, if this was not attained, their final histology report. The results are presented as a Kaplan-Meier survival graph and a table showing 90^{th}, 75^{th}, 25^{th} and 10^{th} centiles and median time from onset of symptoms to development of metaplasia, dysplasia and adenocarcinoma.

Results

Analysis of Symptom Types and Dysplasia and Adenocarcinoma Risk

Of the entire cohort, 1681 patients had information on the types of symptoms suffered prior to the diagnosis of columnar-lined oesophagus. Of these, 1059 were male and 622 were female. The number of patients suffering each of the symptom types (table 8.MT1) is shown in table 8.RT1.

Table 8.RT1 – Proportion of Patients Suffering Each Symptom Type

Symptom Type	N (%) Patients Suffering Symptom Type
Heartburn	1036 (61.6%)
Abdominal Pain	712 (42.4%)
Vomiting etc.	473 (28.1%)
Swallowing	501 (29.8%)
Bleeding	413 (24.6%)
Weight loss	167 (9.9%)
Night-time symptoms	171 (10.2%)

The proportions of males and females in the groups were not significantly different (χ^2 1 degree of freedom) for the symptom groups of heartburn (p=0.604), swallowing symptoms (p=0.204), weight loss (p=0.237) and night-time symptoms (p=0.133). There were, however, differences between the proportion of patients of each gender reporting the symptoms of abdominal pain (44.5% males, 38.7% females: χ^2 1 degree of freedom p=0.024), vomiting etc. (25.8% males, 32.2% females: χ^2 1 degree of freedom p=0.006) and bleeding symptoms (22.5% males, 28.1% females: χ^2 1 degree of freedom p=0.010).

The mean age at diagnosis and mean histological follow-up (including all patients) are shown in tables 8.RT2 and 8.RT3 (compared using independent t-test). Patients suffering from symptoms of heartburn, abdominal pain, vomiting and night-time symptoms were younger at diagnosis than those who did not have these symptoms prior to columnar-lined oesophagus diagnosis, whereas those suffering swallowing symptoms, bleeding symptoms and weight loss were older than those who did suffer these symptoms (table 8.RT2).

Table 8.RT2 – Symptom Type and Age at Diagnosis

Symptom Type	Mean Age of Patients Suffering Symptom	Mean Age of Patients Not Suffering Symptom	p Value
Heartburn	59.9	66.0	<0.001
Abdominal Pain	59.8	64.0	<0.001
Vomiting etc.	61.1	62.7	0.032
Swallowing	63.7	61.6	0.006
Bleeding	68.1	60.3	<0.001
Weight loss	70.1	61.4	<0.001
Night-time symptoms	57.1	62.8	<0.001

The mean follow-up duration was longer in patients who suffered the symptoms of heartburn, abdominal pain, vomiting etc. and night-time symptoms, whereas those suffering bleeding symptoms and weight loss had a shorter follow-up than those who did not (table 8.RT3).

Table 8.RT3 – Symptom Type and Mean Histological Follow-Up

Symptom Type	Mean Follow-Up of Patients Suffering Symptom	Mean Follow-Up of Patients Not Suffering Symptom	p Value
Heartburn	2.63	1.71	<0.001
Abdominal Pain	2.67	1.98	<0.001
Vomiting etc.	2.57	2.16	0.024
Swallowing	2.25	2.28	0.881
Bleeding	1.87	2.41	0.005
Weight loss	1.29	2.39	<0.001
Night-time symptoms	3.78	2.11	<0.001

The year of diagnosis of patients with symptoms of abdominal pain was 0.6 years earlier than those who did not (independent t-test p=0.034), for patients suffering vomiting etc. symptoms was 1.3 years earlier than those who did not (p<0.001), for patients suffering swallowing symptoms was 1.5 years earlier than those who did not (p<0.001), for patients suffering weight loss was 1.3 years earlier than those who did not (p=0.002) and for patients suffering night-time symptoms was 1.5 years earlier than those who did not (p=0.001). There was no significant difference in the year of diagnosis of patients suffering either heartburn (p=0.474) or bleeding symptoms (p=0.909) compared to those patients not suffering these symptoms.

Each of the factors of gender, age at diagnosis and year of diagnosis were controlled for in the analyses of the presence of different symptom types and probability of the finding of dysplasia and adenocarcinoma. Three hundred and seventy one (22.1%) patients developed dysplasia or adenocarcinoma during the course of follow-up. Binary logistic regression was performed entering the covariates listed above and each of the symptom type groups. The result of logistic regression for the finding of all dysplasia is shown in table 8.RT4. There were trends for dysplasia (all grades) and adenocarcinoma to be found more frequently in patients with symptoms of heartburn and weight loss and these findings tended to occur less frequently in patients suffering symptoms of abdominal pain. The odds ratios for the finding of symptoms of bleeding etc. and night-time symptoms were close to 1, indicating no association between these symptoms and the finding of all grades of dysplasia and adenocarcinoma. There were significant associations between the presence of symptoms of vomiting etc. (odds ratio 1.369) and swallowing symptoms (odds ratio 1.695) prior to diagnosis and the finding of all grades of dysplasia and adenocarcinoma (table 8.RT4).

Table 8.RT4 – Logistic Regression of Symptom Type and Development of Dysplasia and Adenocarcinoma

Symptom Type	p value	Odds Ratio	95% CI* for Odds Ratio
Heartburn	0.190	1.196	0.915-1.562
Abdominal Pain	0.547	0.925	0.719-1.191
Vomiting etc.	0.018	1.369	1.055-1.776
Swallowing	<0.001	1.695	1.302-2.207
Bleeding	0.977	0.995	0.724-1.368
Weight loss	0.057	1.435	0.990-2.080
Night-time symptoms	0.913	0.978	0.655-1.460

*CI Confidence interval

One hundred and fifty six patients (9.3%) developed changes of high-grade dysplasia or adenocarcinoma, and a binary logistic regression was performed using the same covariates as above for the development of high-grade dysplasia and adenocarcinoma. There were trends for patients reporting symptoms of abdominal pain (odds ratio 0.735) and bleeding etc. (odds ratio 0.736) to have a lower association with the development of high-grade dysplasia and adenocarcinoma than those patients not reporting these symptoms. Patients

reporting heartburn (odds ratio 0.654) had a statistically significant lower association with the development of high-grade dysplasia and adenocarcinoma than those patients not reporting this symptom group. There was no association between patients reporting vomiting etc. and night-time symptoms and the development of high-grade dysplasia and adenocarcinoma. The symptoms of both swallowing (odds ratio 2.417) and weight loss (odds ratio 2.834) were closely associated with the development of high-grade dysplasia and adenocarcinoma (table 8.RT5).

Table 8.RT5 – Logistic Regression of Symptom Type and Development of High-Grade Dysplasia and Adenocarcinoma

Symptom Type	p value	Odds Ratio	95% CI* for Odds Ratio
Heartburn	0.027	0.654	0.449-0.952
Abdominal Pain	0.119	0.735	0.499-1.082
Vomiting etc.	0.913	0.978	0.657-1.456
Swallowing	<0.001	2.417	1.645-3.553
Bleeding	0.214	0.736	0.454-1.194
Weight loss	<0.001	2.834	1.821-4.410
Night-time symptoms	0.866	1.057	0.557-2.005

*CI Confidence interval

One hundred and twenty nine patients (7.7%) of the cohort developed adenocarcinoma. Binary logistic regression was performed with the same covariates as above and yielded similar results to those for the development of high-grade dysplasia and adenocarcinoma (table 8.RT5).

Table 8.RT6 – Logistic Regression of Symptom Type and Development of Adenocarcinoma

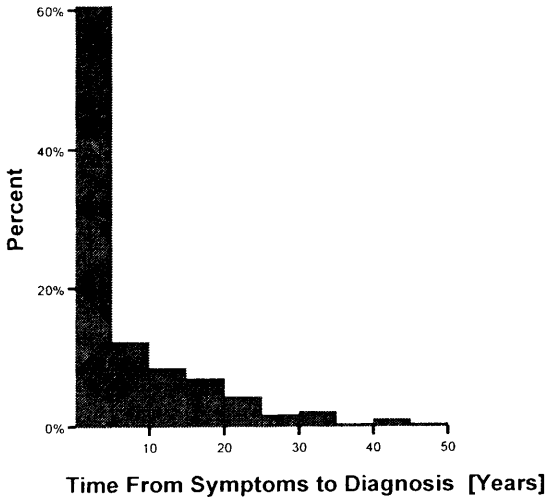
Symptom Type	p value	Odds Ratio	95% CI* for Odds Ratio
Heartburn	0.042	0.654	0.435-0.985
Abdominal Pain	0.118	0.710	0.463-1.090
Vomiting etc.	0.706	0.919	0.592-1.426
Swallowing	<0.001	2.774	1.815-4.239
Bleeding	0.259	0.736	0.432-1.253
Weight loss	<0.001	2.877	1.797-4.606
Night-time symptoms	0.710	0.867	0.408-1.842

*CI Confidence interval

Analysis of Duration of Time from Symptom Onset to Changes of Dysplasia and Adenocarcinoma

The outcome of patients from their onset of symptoms to the first histological demonstration of columnar-lined oesophagus without intestinal metaplasia, columnar-lined oesophagus with intestinal metaplasia, indefinite changes for dysplasia, low-grade dysplasia, high-grade dysplasia and adenocarcinoma were examined using Kaplan-Meier survival analysis. Patients were deemed to have developed the histological changes if a biopsy was taken which demonstrated those changes or changes of greater dysplasia. One thousand and eighty two patients had data available on the duration of symptoms prior to the diagnosis of columnar-lined oesophagus. Of these, the median duration of symptoms prior to diagnosis was 2.59 years. The data were markedly skewed, with a mean of 7.14 years. The range was 1 day to 61.3 years. The duration from symptom onset to diagnosis of columnar lined oesophagus is shown in figure 8.RF1.

Figure 8.RF1 – Duration of Symptom Onset to Diagnosis of Columnar-Lined Oesophagus



There was a trend for the mean duration of symptoms prior to diagnosis to be longer in patients with dysplasia at diagnosis compared to non-dysplastic columnar-lined oesophagus, but the mean duration of symptoms of patients who had adenocarcinoma at their diagnostic biopsy was shorter (one way analysis of variance p=0.360 comparing all 6 diagnostic histology groups). The mean duration of symptoms grouped by diagnostic histology is shown in table 8.RT7.

Table 8.RT7 – Mean Duration of Symptoms at Diagnosis of Columnar-Lined Oesophagus Grouped by Diagnostic Histology

Diagnostic Histology	N Patients	Mean Symptom Duration [Years]	95% CI* for Mean Symptom Duration
CLO-†	332	6.9	5.9-8.0
CLOIM†	508	7.4	6.5-8.3
Indefinite for Dysplasia	90	6.7	4.9-8.5
Low-Grade Dysplasia	82	7.6	5.6-9.6
High-Grade Dysplasia	11	12.0	4.0-20.0
Adenocarcinoma	59	5.4	3.0-7.8

*CI Confidence interval
†CLO- Columnar-lined oesophagus without intestinal metaplasia
†CLOIM Columnar-lined oesophagus with intestinal metaplasia

The most dysplastic histology attained by patients during the course of follow-up is shown in table 8.RT8.

Table 8.RT8 – Most Dysplastic Histology Attained by Patients during the Course of Follow-Up

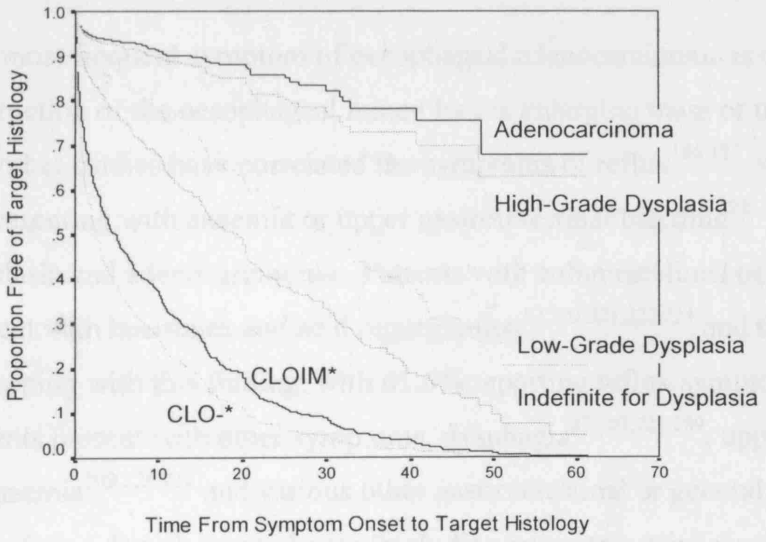
Most Dysplastic Histology Attained	N (%)Patients
CLO-*	197 (18.2%)
CLOIM*	459 (42.4%)
Indefinite for Dysplasia	150 (13.9%)
Low-Grade Dysplasia	159 (14.7%)
High-Grade Dysplasia	21 (1.9%)
Adenocarcinoma	96 (8.9%)

* CLO- Columnar-lined oesophagus without intestinal metaplasia
* CLOIM Columnar-lined oesophagus with intestinal metaplasia

Figure 8.RF2 shows the survival curves for the development of all columnar metaplasia with and without intestinal metaplasia, indefinite changes for dysplasia, low-grade dysplasia, high-grade dysplasia and adenocarcinoma. Subjects examined on each curve were deemed to have had the "event" of developing that grade of dysplasia if that grade of dysplasia or a more dysplastic grade of dysplasia was demonstrated. The origin of the time axis is the onset of symptoms.

The time from symptom onset to the development of each of the histological changes is shown in table 8.RT9 as determined by Kaplan-Meier survival analysis.

Figure 8.RF2 – Survival Curves of Patients from Symptom Onset to Development of Metaplasia, Dysplasia and Adenocarcinoma



* CLO- Columnar-lined oesophagus without intestinal metaplasia
* CLOIM Columnar-lined oesophagus with intestinal metaplasia

Table 8.RT9 – Time for Patients to Develop Histological Features of Metaplasia, Dysplasia and Adenocarcinoma from Onset of Symptoms

Target Histology	90th Centile*	75th Centile*	Median*	25th Centile*	10th Centile*
CLO-†	0.1	0.5	2.6	10.5	20.5
CLOIM†	0.2	0.9	5.0	15.6	26.6
Indefinite†	0.8	6.0	19.3	35.1	49.8
LGD†	1.5	11.3	30.0	-§	-§
HGD†	9.6	32.0	-§	-§	-§
AC†	13.8	48.4	-§	-§	-§

* Time [Years] for patients remaining in cohort who had not attained target histology changes or changes of greater dysplasia
† CLO- Columnar-lined oesophagus without intestinal metaplasia
† CLOIM Columnar-lined oesophagus with intestinal metaplasia
† Indefinite Indefinite changes for dysplasia
† LGD Low-grade dysplasia
† HGD High-grade dysplasia
† AC Adenocarcinoma
§ Centile point not reached during the course of follow-up

Discussion and Conclusions

Symptom Type and Association with Dysplasia and Adenocarcinoma

The most frequent symptom of oesophageal adenocarcinoma is dysphagia due primarily to obstruction of the oesophageal lumen by the enlarging mass of the carcinoma[69;221;291;292], and other studies have correlated the symptoms of reflux[186;187], weight loss[292] or nausea[292] or presenting with anaemia or upper gastrointestinal bleeding[221;292] with the development of dysplasia and adenocarcinoma. Patients with columnar-lined oesophagus most frequently present with heartburn and acid regurgitation[82;203;221;222;224] and the results of this study are in keeping with this finding, with 61.6% reporting reflux symptoms. Less frequently, patients present with other symptoms: dysphagia[82;203;221;289], upper gastrointestinal bleeding or anaemia[203;221;222] and various other gastrointestinal or general symptoms[203;222]. This study found that abdominal pain (including epigastric pain) was the second most frequent presenting symptom (present in 42.4% of patients), with 29.8% of patients complaining of swallowing problems, 28.1% complaining of symptoms of nausea and vomiting and 24.6% of patients presenting with upper gastro-intestinal bleeding or anaemia. Only 10.2% of patients in this cohort presented with nocturnal symptoms and 9.9% presented with weight loss. The symptoms of swallowing problems (odds ratio 1.695) and vomiting (odds ratio 1.369) were significantly associated with the development of all grades of dysplasia and adenocarcinoma, with trends for the symptoms of heartburn and weight loss to also be associated with the development of all grades of dysplasia and adenocarcinoma. The presence of swallowing symptoms and weight loss had strong associations with the development of high-grade dysplasia and adenocarcinoma together or adenocarcinoma alone. Symptoms of heartburn actually had an inverse association with the development of high-grade dysplasia or adenocarcinoma within this cohort. This is not in agreement with Lagergren's findings[39], but may be explained by the different reference population: patients who were known to have columnar-lined oesophagus in this study and the general Swedish population in Lagergren's study. The presence of nocturnal reflux symptoms was not associated with the development of columnar metaplasia in one series[224] (unlike its association with oesophageal adenocarcinoma[39]), and this study did not demonstrate any significant association with the development of dysplasia or adenocarcinoma. There were variations between patients reporting the presence or absence of different symptom groups

in age at diagnosis and follow-up time, but these factors were controlled for in the logistic regression. The durations of different types of symptoms were not stored separately in the database, which did not allow for the duration of specific symptom types to be analysed in the development of metaplasia, dysplasia or adenocarcinoma and, for the same reason, the duration of follow-up was not included in the analysis as a covariate.

Duration of Symptoms and Metaplasia-Dysplasia-Adenocarcinoma Sequence

The pathway from normal squamous mucosa to development (sequentially) of inflammation, columnar metaplasia (including the development of intestinal metaplasia) and progression to dysplasia and adenocarcinoma has been shown by studies which examined the magnitude of gastro-oesophageal reflux (lowest in non-erosive reflux disease, and progressively higher in reflux oesophagitis, columnar metaplasia, dysplasia and highest in oesophageal adenocarcinoma)[154;224;227;248], but there are few data on the time scale of development of these changes. The overall incidence of adenocarcinoma in patients who have already developed columnar metaplasia is 0.69% (see appendix 1) and higher rates have been reported in patients with low-grade dysplasia[47;95] and high-grade dysplasia[90;277]. Other studies have demonstrated the development of intestinal metaplasia over time in patients who previously did not have goblet cells[67;87;186;250;252] and subsequent development of dysplasia and adenocarcinoma in these patients[87], but most patients did not develop dysplasia or adenocarcinoma within the study periods. The development of oesophageal adenocarcinoma has also only occurred in patients with previous dysplasia in some series[92-94]. Frequently there are areas of dysplasia surrounding the tumour itself in studies on resected oesophageal adenocarcinomata[22;29;44-51]. Patients with persistent symptoms despite treatment of gastro-oesophageal reflux disease have also been reported to be at a higher adenocarcinoma risk[186;289]. These data support the hypothesis that there is a pathway in time from the onset of symptoms of gastro-oesophageal reflux disease to the development of metaplasia, dysplasia and finally adenocarcinoma; however, fortunately the majority of patients with gastro-oesophageal reflux disease do not progress down this pathway as far as the development of adenocarcinoma[221] and many do not progress to the development of columnar metaplasia[59;77;79-83;150]. Examining only the diagnostic histology of patients in this series showed that there was a trend for a longer duration of symptoms in patients with non-dysplastic columnar metaplasia who had intestinal metaplasia over those patients who

did not have intestinal metaplasia. There was a trend for patients with dysplasia to have longer symptom duration than those without dysplasia, but patients who had adenocarcinoma at columnar-lined oesophagus diagnosis had the shortest mean average duration of symptoms, possibly due to patients only reporting their most acute symptoms, or due to these patients having asymptomatic reflux. For the majority of patients, the presence of symptoms correlates well with the presence of pathological gastro-oesophageal reflux[186]. However, series have demonstrated that a significant proportion of patients do not have upper gastrointestinal symptoms at diagnosis of columnar-lined oesophagus[82:221:290] and the patients seen in surveillance programmes for follow-up of columnar-lined oesophagus represent only a fraction of the numbers suggested by an autopsy study[72] or screening studies of asymptomatic individuals[78]. Other studies have shown that a large proportion of patients with gastro-oesophageal reflux disease who are asymptomatic on antireflux medications still have pathological reflux[124:129:130] and this would further support the hypothesis that many patients have asymptomatic reflux or are under-reporting their reflux symptoms. The distribution of symptom duration was markedly skewed, with the majority of patients reporting symptoms for under 7½ years prior to columnar-lined oesophagus diagnosis, but a mean duration of 2.59 years. The Kaplan-Meier survival analysis showed that the median time (duration of symptoms at which half of the cohort had developed the histological changes) to diagnosis of columnar-lined oesophagus was 2.6 years, to columnar-lined oesophagus with intestinal metaplasia was 5.0 years, to indefinite changes for dysplasia was 19.3 years and low grade dysplasia was 30.0 years. The median centile point for development of high-grade dysplasia or adenocarcinoma was not reached in this cohort, but the time for the 90th centile point (the time within which 10% of the cohort followed to this point had developed the changes of high-grade dysplasia or adenocarcinoma) was 1.5 years for all dysplasia and adenocarcinoma, 9.6 years for high-grade dysplasia and adenocarcinoma and for adenocarcinoma alone was 13.8 years.

Other Sources of Error in This Study

The study had lower power to detect changes associated with high-grade dysplasia or adenocarcinoma (only 10.8% of patients developed these changes) compared to less dysplastic changes. Consequently there was scope for a type II statistical error, which was

highest in the analyses for high-grade dysplasia or adenocarcinoma. The analyses did not examine for the development for prevalent or incident histological changes separately, and could only demonstrate associations between symptom types or duration and development of different histological findings, rather than prove a causal effect. Patients may only have reported the duration and types of their most acute symptoms rather than more chronic symptoms, which will have contributed to the skewed nature of the data, and the fact that the mean duration of symptoms at diagnosis was shortest in patients with adenocarcinoma at diagnosis (compared to all other diagnostic histology groups) also supports this hypothesis. Variations in biopsy protocol[184;197;253-255;275], follow-up protocol[100;244] and histopathological interpretation[95;189;280-282] are also potential sources of bias in this study and have been discussed in chapter 6.

Chapter 9 - Validity of Data

Introduction

There are a number of errors which occur in surveillance studies of this kind. These may be separated into errors of all surveillance cohort studies, errors specific to this type of retrospective observational study and particular problems associated with this study. To validate the data used to conduct the study, 2 specific exercises have been undertaken: firstly recalling hospital records to examine whether the same information was available at separate instances in time when these notes were requested from filing, and secondly by re-entering the data from patients' records to examine for interobserver variability in this process.

Errors Occurring in Surveillance Cohort Studies

Design of Study

The plan for this study was conceived prior to the enrolment of participating centres, and as with many multicentre studies, the study period (both the time period of recruitment of patients into the study and period during which these patients underwent surveillance) varied between the centres preventing much comparison of outcome between centres (this was also compounded by the small numbers of events/carcinomata at each centre causing a study between centres to be underpowered). The database template was only designed 6 months after the author's involvement in the study, but the blanket-data collection (amassing any useful data from hospital records) will have minimised any missing data on this account. If time had permitted, it would have been preferable to complete design of the study (following a pilot study) prior to data accrual for the registry and natural history study.

Study Population Choice

The evidence that patients with columnar metaplasia are the most appropriate population to study as those at highest (known) risk of oesophageal adenocarcinoma development[22;29;42-

[51;86;89;92;167-169] is described in the review chapter, but prospective controlled studies to demonstrate a clear difference in risk between study populations such as this one and control groups have not been satisfactorily carried out.
The study population was initially designed to involve any patients deemed to have columnar metaplasia of the oesophagus as determined by that particular centre, but to ensure that the these patients did have true oesophageal columnar metaplasia, and were not being mis-diagnosed by their participating centre, the individual studies on the behaviour of the columnarised segment required both endoscopic and histological confirmation of the presence of a metaplastic segment.

Diagnostic Criteria and Tests

As has been stated, the mainstay of diagnosis of columnar metaplasia of the oesophagus is by upper alimentary endoscopy and biopsy. Despite the strong association with the most severe gastro-oesophageal reflux disease[59;61;67;68;81;149-151], symptom presence is not a reliable predictor of the presence of columnar metaplasia[290], and many subjects with oesophageal columnar metaplasia are asymptomatic or will never be diagnosed[78]. Consequently, although the symptomatic population are likely to undergo upper gastrointestinal endoscopy[91] for diagnosis, this does not necessarily imply that these patients will subsequently undergo surveillance and the majority of patients with columnar-lined oesophagus will never be diagnosed[72]. Subsequently, the conclusions drawn from studies of this kind where only a subset of the total population with the condition will be diagnosed, may not necessarily hold for the remainder of the "silent" population.

Diagnostic and Surveillance Test Accuracy

As has been discussed, there is considerable inter- and intra-observer variability in the measurement of the columnarised oesophageal segment[197-200] and the histopathological interpretation of biopsy specimens[95;189;280-282]. In addition to the observer variabilities, the process of biopsy sampling is also subject to significant sampling error[197;252-255] as well as variability in protocol between centres. Subsequently, the diagnostic and surveillance tests lack significantly in sensitivity, specificity and reproducibility.

Completeness of Registration Process

The centres involved in the study used the most appropriate local protocol for identifying patients with columnar-lined oesophagus for registration. Some prospectively collected patients each time a columnarised segment was discovered at endoscopy at the same time as the follow-up endoscopy was booked. Others searched their endoscopy or histology databases at periodic intervals for all cases labelled as "Barrett's oesophagus" or oesophageal columnar metaplasia. The ethical permission for this study did not allow registry researchers to search for missing cases by any means.

Differences in Management

As an observational study, the population involved in this study had no uniform management strategy either for surveillance policy or treatment of the pre-malignant disease. Differences between surveillance management and outcome have been examined by another student. The management strategy for patients with columnar-lined oesophagus varied both between the centres involved and time period during which the patients were treated (as shown in chapter 7). Furthermore, the type and dosing regimen of the main anti-reflux medications employed varied between centres.

Patient Non-Compliance with Treatment

Only a carefully designed prospective study could examine patient compliance with prescribed anti-reflux medication and compliance tends to be poor (although medication use tends to reflect symptom severity[335]). Subsequently, this study could not accurately examine the actual acid suppression therapy being taken by the patients (and even patients taking large doses of proton pump inhibitors may still have significant acid reflux[124;129;130;153;154]). Additionally, patients with upper-gastrointestinal symptoms self-medicate significantly[335]. Anti-reflux surgery does not require a similar prolonged patient compliance (but does have a significant early and late failure rate)[133;138]. Whichever management strategy is employed for individual patients must bear in mind the short-comings of each treatment type and likely individual patient compliance with that therapy

especially in the light that there is no clear benefit from medical over surgical anti-reflux therapy (or vice-versa)[136;137].

Non-Compliance with Surveillance

Patients may also not comply with surveillance programmes, which in part is due to the age and co-morbidity of the population with oesophageal columnar metaplasia. Patients may also opt out of surveillance programmes especially as they become better educated about the relatively small risk of malignancy associated with the metaplastic segment and limited efficacy of treatment if adenocarcinoma were to develop[8;69] and this is addressed in the British Society of Gastroenterology guidelines[121]. Additionally, physicians may not offer surveillance to patients who they deem to be at lowest risk of developing oesophageal malignancy, or those too frail to undergo an oesophageal resection[279]. The development of effective less invasive therapies for high-grade dysplasia and superficial adenocarcinoma[115;116] demands re-evaluation of surveillance if early cancer or high-grade dysplasia can be reliably detected and treated.

Incomplete Hospital Records

Unfortunately, hospital records are not complete accounts of patients' health. They often do not contain information from patients' general practitioners or from endoscopies or treatment undertaken at other hospitals. By their nature, hospital notes are subject to errors in recording and filing. Sets of notes may be hoarded and unavailable for examination, transferred to microfiche (with varying degree of diligence and completeness in the process), lost or destroyed. Some centres excelled at maintaining complete records of all treatment of columnar lined oesophagus and outcome of treatment for adenocarcinoma; whereas, in other cases, patients were referred to a tertiary centre for management of adenocarcinoma and no further information was available. The future ability to determine patients' mortality (see below) will improve this situation, as will further development of electronic patient records, allowing more reliable access to hospital notes.

Determination of Outcome

The most appropriate outcome measures in this type of study should be development of oesophageal adenocarcinoma and all-cause mortality. Unfortunately, due to the flaws in the data collection mechanisms described above, outcome at the time of data accrual for form 2 was not complete to that final date and the last hospital visit for endoscopy and biopsy was consequently employed as the most recent follow-up date. Due to the relatively static populations studied and regular visits to the centre undertaking columnar-lined oesophagus surveillance, the number of patients who developed adenocarcinoma and were lost to follow-up should be small, but there were a significant number of patients whose final outcome was not clear. All-cause mortality is an extremely important outcome measure in this type of study and a mortality "flagging" study (where on the occasion of a patient's death, a copy of their death certificate will be sent to the research institute) on a subset of this cohort is currently being undertaken. The other significant confounding factor which altered the natural history of the metaplastic segment was of prophylactic treatment of ablation of a dysplastic segment or resection of high-grade dysplasia. Consequently, secondary end-points of the development of all grades of dysplasia or high-grade dysplasia have also been used in this study. One hundred and eighty nine patients had documentation of discontinuation of surveillance. Some of these patients had multiple factors involved in this decision and the reasons for ceasing surveillance are stated in table 9.IT1.

Table 9.IT1 – Reasons for Discontinuation of Surveillance of Columnar-Lined Oesophagus

Reason for Discontinuing Surveillance	No. Patients
Non-circumferential segment	4
Technical Difficulty/Intolerance of Endoscopy	7
Comorbidity	35
"Stable Disease"	16
Short Segment Disease Only	30
Age	57
Regression of Segment	27
Referral to Tertiary Centre	1
Patient Choice	6
Patient Move Out of Area	13
Patient Did Not Attend	7
Asymptomatic Patient	5
Unknown	19

This has demonstrated that the most frequent reasons for ceasing surveillance were patient age and comorbidity. In 27 cases, there had been apparent regression of the columnarised segment (either partial or complete) and so no follow-up was believed to be necessary in the light of a presumed lower malignant potential of the segment. In 34 patients, the presence of either short segment disease or non-circumferential disease was deemed to be of low malignant potential and so not warrant surveillance. Only 13 patients had their surveillance discontinued due to technical difficulties with endoscopy or patient choice not to pursue surveillance and 7 were discharged from surveillance after failure to attend for endoscopy or outpatient appointments. Overall, these patients made up 6.9% of the entire cohort, but this will not necessarily account for all patients lost to follow-up.

Absence of a Non-Columnar-Lined Oesophagus Control Population

There was no immediately available control population for comparison with those patients known to have oesophageal columnar metaplasia. Consequently, comparisons were made between subsets of the cohort. A comparable population without columnar-lined oesophagus would help to validate that the correct cohort was being studied i.e. those at highest risk of developing adenocarcinoma of the oesophagus. A control cohort could also have helped remove confounding effects of some of the variables such as age. This does

not in any way undermine the results produced by this study, but it must be borne in mind that all comparisons made are between different patients who have been diagnosed with columnar-lined oesophagus.

Errors Occurring in Retrospective Observational Studies

The fact that this study was conducted in a mainly retrospective (rather than completely prospective) fashion during a period before national guidelines have been published will perhaps have resulted in more variation between different patients as far as criteria for diagnosis, treatment protocol and follow-up protocol are concerned.

Specific Problems Associated With This Study

The multicentric nature of the study without uniform diagnostic criteria and management strategies also will have introduced further variability between management in the same areas as discussed in the paragraph above "Errors Occurring in Retrospective Observational Studies". A total of 19 histopathologists and 35 endoscopists were involved in the management of the study population.

Errors in Data Extraction from Hospital Records

Introduction

Examining large numbers of hospital records is a time consuming and tedious process. Consequently, there will be human error involved in the data extraction process. A small sample of clinical records was recalled for examination on a separate occasion after the initial "form 2" data collection by a second (blinded) observer. This allowed the whole process of data accrual from notes to be examined – from the files being extracted from the hospital medical records office through to the "form 2" data taken back to the registry.

Methods

The notes of 10 study subjects were chosen at random from 3 centres and after completion of the initial study data collection, these hospital records were re-examined in the same fashion as previously in the main natural history study. The presence of data items available from the first and second extractions was examined and agreement was analysed. Data extraction on the 2 occasions was undertaken by combinations of all 3 researchers involved in data extraction in the natural history study. This process was done both for all types of data item and then analysed in subgroups as defined in table 9.MT1. If there was disagreement between the data items extracted at the 2 separate times, for example different weights or medications documented in the notes at the 2 times of data extraction, this was also noted.

Table 9.MT1 – Data Subtypes for Analysis

Data Type Subgroups	Data Items
Registration	Name Gender Date of Birth Hospital Number NHS Number
Demographics and Epidemiology	Occupation Weight on a Specific Calendar Date Height Smoking Habit Alcohol Consumption Marital Status
Endoscopy	Endoscopy Report
Histology	Histology Report
Medication Use	Record of Medication Use On a Specific Calendar Date
Past Medical History	
Symptoms	Symptom Type Symptom Onset
H Pylori	Date of H Pylori Test Type of H Pylori Test Result of H Pylori Test

Results

The median time between examination of sets of hospital records was 0.63 years (range 0.39-5.19 years). All except one set of records in this study were re-examined within one year of the original examination. A total of 273 different items of information were found between the 2 sets of examinations. A total of 10 (3.7%) of these items would not have been available at both sets of examinations of the hospital records due to the fact that they occurred after the first examination of the hospital records (occurring in 4 of the 10 patients). These 10 items are excluded from subsequent analyses.

At second data extraction from the patients notes, 173 (65.8%) of the 263 total items of data were found at both examinations. The range was 15/29 (51.7%) to 28/36 (77.8%). When the type of data item extracted was examined, the analysis demonstrated that there was a large degree of variability between consistency of data types at the 2 extractions (table 9.RT1). Registration data was most consistent between the data extractions, with

endoscopy, past medical history and H pylori (small numbers) also being found to have ≥80% of data items found on both extractions. Histological records were less consistently found on both data extractions (71.4%) and the consistency of demographic and epidemiological data, medication use and symptoms were poorest at ≤50%.

Table 9.RT1 – Data Availability at Extractions by Data Type Subgroup

Data Type Subgroups	Data Items Present at Both Extractions
Registration	37/39 (94.9%)
Demographics and Epidemiology	34/82 (41.5%)
Endoscopy	33/37 (89.2%)
Histology	20/28 (71.4%)
Medication Use	11/25 (44.0%)
Past Medical History	27/33 (81.8%)
Symptoms	7/14 (50.0%)
H Pylori	4/5 (80.0%)
Total	173/263 (65.7%)

The data extracted at both times were the same except on 3/263 (1.1%) occasions. These occurred when two patients changed their names after getting married/divorced, and one patient's civil status changed prior to diagnosis of columnar-lined oesophagus, but this was only recorded at the second data extraction. There was no disagreement between any of the other data items comparing data extracted at first and second examinations.

Discussion and Conclusions

This study has demonstrated that the data items available at two examinations of patients' hospital records were more consistent in some data subtypes than others. The most consistent areas were registration, endoscopy, H pylori and histology. These are the core data items which were involved in almost every chapter of this thesis. The data are poorer for the recording of medication use and epidemiological data. The potential for errors generated by the absence of these data items at one point in time will be reduced by the way in which the analyses were performed. The analyses examined for all medication use, tobacco use, alcohol consumption, weight measurements and height measurements over the period preceding or following diagnosis and so absence of one measurement would only rarely cause a change in the group a patient was included into as patients frequently had

multiple records of these data items within the study period. Discrepancies in data extraction will have been caused by problems with hospital record retrieval from the medical records department (retrieval of temporary sets of notes, incomplete notes, multiple volumes of notes only partially retrieved, loss of notes and loss of individual or groups of sheets of data from hospital records) or observer errors in extraction of data items.

Errors in Data Entry into the Database

Similarly to the initial data extraction to produce "form 2", the accuracy of the process of data entry was examined in a small group of study subjects.

Methods

The "form 2"s of 10 study subjects were selected at random and the data were re-entered into the database in exactly the same way as in the main natural history study. The entered data were then examined for consistency looking at the agreement between first and second data entries from each form 2 into the database. The agreement was examined firstly for consistency of records (e.g. an endoscopy or histology report) being entered on both occasions, secondly to examine the overall agreement between first and second data entries for the all data entered (including records where the data had only been entered on either the first or second occasion) and finally the data entry agreement was examined only for records which had been entered on both occasions. The data are presented grouped by data table and for all data.

Results

The consistency for data record entry is shown in table 9.RT2. The agreement between entry of entire records was excellent (100%) for the General Information parent table and weight tables. The agreement for entry of endoscopy and histology records was above 90% indicating close agreement between both sets of examination of the "form 2" data. Agreement was poorer for alcohol consumption, smoking habit, medication use and H pylori (small numbers) at between 50% and 70%. The overall agreement was 81.8%.

Table 9.RT2 – Agreement for Whole Record Entry into Database

Table	No. of Records	No. of Records in Agreement
Alcohol Table	12	8 (66.7%)
Endoscopy Table	40	39 (97.5%)
General Information Table	10	10 (100%)
Histology Table	28	26 (92.9%)
H Pylori Table	2	1 (50.0%)
Medication Table	36	20 (55.6%)
Smoking Table	16	11 (68.8%)
Weight Table	15	15 (100%)
Overall	**159**	**130 (81.8%)**

The overall agreement for data entered onto the database is shown in table 9.RT3. Agreement was 86.2% for all data entered comparing first and second data entries from the same "form 2" information. The closest agreement was between data in the General Information table, Endoscopy table and Weight table at >90%. Agreement for records in the Histology table was 88.6%. Agreement for data in the Alcohol, Smoking and H Pylori (very small number of data) tables was poorer at 50%-62.5%. The lowest agreement was seen in the medication table at 46.7%.

Table 9.RT3 – Overall Agreement for Data Re-Entry into Database

Table	No. of Records	No. of Records in Agreement
Alcohol Table	24	14 (58.3%)
Endoscopy Table	801	750 (93.6%)
General Information Table	1000	944 (94.4%)
Histology Table	588	521 (88.6%)
H Pylori Table	6	3 (50.0%)
Medication Table	362	169 (46.7%)
Smoking Table	32	20 (62.5%)
Weight Table	30	29 (96.7%)
Overall	**2843**	**2450 (86.2%)**

After excluding data which had only been entered by one of the two observers, the overall agreement was 93.5%. Agreement was above 90% for Endoscopy, General Information, Histology, Smoking, Weight and H Pylori table data. Agreement for the Alcohol table was 87.5% and was lowest for the Medication table at 78.3% (table 9.RT4).

Table 9.RT4 – Agreement for Data Re-Entry into Database after Exclusion of Data Entered by Only One Observer

Table	No. of Records	No. of Records in Agreement
Alcohol Table	16	14 (87.5%)
Endoscopy Table	781	746 (95.5%)
General Information Table	1000	944 (94.4%)
Histology Table	546	518 (94.9%)
H Pylori Table	3	3 (100%)
Medication Table	212	166 (78.3%)
Smoking Table	22	20 (90.9%)
Weight Table	30	29 (96.7%)
Overall	**2610**	**2440 (93.5%)**

Discussion and Conclusions

This study has demonstrated that the agreement for data entered on the database was over 90% for data entered by both observers. However, there was a greater discrepancy between observers' entry of data when the whole process of data entry from "form 2" onto the database was examined. When the whole process was examined, the agreement between the two observers was 86.2% overall, with both observers entering the whole data records in 81.8% of cases. The areas demonstrating the highest levels of agreement are likely to be those where there were a large proportion of null data or Boolean data (true/false or yes/no). Data stored as free text will have the lowest level of agreement. The areas of greatest agreement occurred in the General Information, Endoscopy, Histology and Weight tables. These are the parts of the database used most frequently in the analyses performed – as was seen in the re-examination of notes to produce "form 2". This finding has demonstrated that the overall agreement and subsequent accuracy of the database is highest in the areas involved most frequently in the analyses. The fact that frequently the design of the queries examined data over a period of time will have further minimised errors in a single record or data item that will have altered the outcome for a patient in any particular analysis.

Diagnosis and Inclusion Criteria

Unlike other studies which have been based on a short period of time during which data were collected on subjects, this study had the ability to examine patients' clinical course prior to and following the registration date. This allows more accurate conclusions to be drawn concerning the date of diagnosis and follow-up period than a study examining a population only over a specific time period.

Database Query Design to Extract Data for Analyses

Each database query was written to select appropriate patients for analysis depending on whether they had data available which would allow them to be appropriate for inclusion in each particular analysis (e.g. segment length measurements and corroborating endoscopic and histological appearances). Queries then examined the data which varied over time. After construction of each query, the data produced were examined to ensure that they had been appropriately selected and manipulated by carefully examining the output data and the effects of altering data and then re-running the query to check that the query had handled a change in the data correctly. This has been described further in chapter 2 Data Errors section.

Statistical Analysis

The choices of statistical analyses are described in Chapter 3 (statistical analyses section). The analyses have been performed using a small number of consistent statistical tests to minimise methodological errors and ensure that the choice of statistical analysis had not been altered in an attempt to bias the results produced and conclusions drawn.

Outcome Measures

The number of patients who developed adenocarcinoma in this cohort is small. Unfortunately, this makes statistical examination of the rate of adenocarcinoma problematic, in particular examining for interactions between variables whilst analysing these sparse data. Consequently, other (secondary) end-points have also been employed as

described above in the "Determination of Outcome" paragraph. Although these measures are not the hard endpoints of development of oesophageal adenocarcinoma or death, they are valid secondary endpoints as the metaplasia-dysplasia-adenocarcinoma pathway has been demonstrated over time[92-94].

Power of Study

The study was designed to have a power of 80% to detect a difference of 50% in the proportion of patients developing adenocarcinoma within two groups of at least 904 patients (with proportions of the groups developing adenocarcinoma of 5% and 2.5%). The numbers of patients in the total cohort was 2751. The total sample size for alcohol, smoking and body mass index analyses all fell below this number (chapter 4). The total number of patients in the segment length analyses (chapter 4) was 1389 (split into 4 groups). There were 1329 patients involved in the histological analysis (split into 5 groups, chapter 6). The treatment analysis (chapter 7) involved 864 patients (split into 6 groups). One thousand six hundred and eighty one patients were involved in the symptom analyses (split into 7 groups, chapter 8). These studies will all subsequently have been underpowered by the sample size involved in the groups. The power of the study has been increased by prolonging the period of follow-up between groups in the survival analyses, but as many patients did not have the required data to be involved in the analyses or surveillance follow-up data, the original estimate from the power calculation did not adequately power many of the studies using the defined α and expected differences between groups. Additionally, as multiple analyses were performed on the same data, with a value of $\alpha=0.05$, there is a possibility of type I statistical error.

Strengths of This Study

The study was designed to be robust in its examination of the natural history of columnar-lined oesophagus in its behaviour in clinical practice at multiple centres throughout the United Kingdom. The requirements of the design of the individual analyses of data for chapters 4-8 maintained that only appropriate patients were involved. To maximise the power of analysis of different outcomes between groups (with varying treatment regimens and follow-up), the groups were kept as large as possible, whilst endeavouring to separate

patients appropriately on clinical grounds. The use of appropriate secondary endpoints (which occur more frequently than the primary endpoints) will also have increased the power of the study to reach those endpoints. The small proportion of patients who were known to be discharged from follow-up also adds to this study's strength. The analyses of interobserver agreement in data extraction and entry demonstrated 65.7% agreement in the process of data extraction following request of medical records to transcription of data onto "form 2" and 86.2% agreement in entry of "form 2" data onto the database. The design of queries, processes of searches for data errors and statistical analyses were also robust.

Chapter 10 – Summary of Findings, Contribution to Medical Science and Future Studies

This is the largest in-depth study of a cohort of patients with columnar-lined oesophagus described and second largest study of adenocarcinoma development in this disease (the largest being from a histopathology database[216]). The study is on-going with continued follow-up of the cohort and recruitment of new patients.

General Demographics and Epidemiological Associations

This study has clarified the epidemiological associations of columnar-lined oesophagus. It has demonstrated that in the United Kingdom the clinical picture of columnar-lined oesophagus does not mimic that reported in the United States with a lower male to female ratio than reported there, but which is uniform throughout the studied centres. In agreement with other studies, adenocarcinoma (prevalent and incident) was more common in older patients, and prevalent adenocarcinoma more common in males than females and smokers compared to non/ex-smokers. There was no association between smoking or gender and the development of incident adenocarcinoma. These findings support previously published epidemiological data on columnar-lined oesophagus and oesophageal adenocarcinoma.
In this cohort as the number of diagnostic and surveillance endoscopies increased throughout the study period, the proportion of prevalent adenocarcinoma in columnar-lined oesophagus as a proportion of all new diagnoses of columnar-lined oesophagus was falling, but the rate of development of incident carcinoma remained constant throughout the study period.
The overall adenocarcinoma incidence was 1 in every 170 patient-years of follow-up (which is in agreement with the literature) and annual incidence of high-grade dysplasia and adenocarcinoma combined was 1 in every 100 patient-years follow-up (on which there is very little published research).
This study has helped to clarify the epidemiological associations of columnar-lined oesophagus and its overall rate of progression to adenocarcinoma.

Length of Metaplastic Segment Length Experiments and Adenocarcinoma Risk Based on Diagnostic Histology

The segment length analysis has demonstrated that there is variability in the length of segment measured at endoscopy; however, only a minority of patients appeared to demonstrate a consistent increase or decrease in segment length when followed-up for at least 5 years and changes in length did not correlate with any difference in clinical course, which opposes views that increase in length are associated with a poorer prognosis and regression of the segment is indicative of a lower neoplastic potential. Longer segments of columnar-lined oesophagus were associated with older age at diagnosis and the finding of dysplasia within the segment. When the study group was analysed controlling for the confounding effects of age at diagnosis, gender and diagnostic histology, there was a trend for higher adenocarcinoma risk in longer segments but this did not reach statistical significance.

In this analysis of patients with a segment length measurement, there was a higher risk of development of adenocarcinoma and high-grade dysplasia in patients who had low-grade dysplasia compared to columnar-lined oesophagus without intestinal metaplasia, but no statistically different risk when comparing either columnar-lined oesophagus with intestinal metaplasia or changes indefinite for dysplasia to non-dysplastic columnar-lined oesophagus without intestinal metaplasia.

This study has demonstrated that the major risk determinants of high-grade dysplasia and adenocarcinoma development in columnar-lined oesophagus are patient age and presence of dysplasia, with adenocarcinoma developing in all segment length groups (including short segment) and without intestinal metaplasia on the diagnostic biopsies, consensus on which has not yet been reached previously.

Histological Fate of the Metaplastic Segment and Implications for Surveillance

The histological surveillance study has demonstrated that the risk of development of high-grade dysplasia or adenocarcinoma at 10 years of follow-up in non-dysplastic columnar-lined oesophagus with or without intestinal metaplasia is 5.4% and 6.5% respectively. These two groups of patients behaved in a similar fashion, and at 3 years of follow-up more than half of patients who had initially not been found to have intestinal metaplasia had

subsequently demonstrated this histologically (median time to the finding of intestinal metaplasia 2.3 years). At 10 years of follow-up, over 90% of patients had demonstrated intestinal metaplasia and this finding was also dependent on the number of biopsy samples taken. This finding is in contradiction to the United States guidelines on the management of columnar-lined oesophagus as it does not support the presence or absence of intestinal metaplasia as a useful marker of neoplastic risk and grounds for inclusion or exclusion into a surveillance programme. Following the finding of low-grade dysplasia, 7.8% of patients had developed adenocarcinoma within 5 years and 10.6% had developed either high-grade dysplasia or adenocarcinoma within this period, which was 3-4.5x that of non-dysplastic columnar-lined oesophagus. In the patients with high-grade dysplasia who were followed-up clinically, over half had developed adenocarcinoma within one year. These data produce a clear model of the expected detection rate of dysplasia and adenocarcinoma at different surveillance intervals, which will result in a more evidence-based approach to planning of surveillance programmes.

Medical and Surgical Control of Gastro-Oesophageal Reflux and Risk of Dysplasia and Adenocarcinoma in Patients who had Undergone Gastric Outlet Surgery

The medical and surgical control of reflux yielded similar rates of development of dysplasia and adenocarcinoma.

This study would not support surgical procedures over medical therapy in the control of gastro-oesophageal reflux with the exception of not treating with a histamine H_2 receptor antagonist alone (which had a higher rate of development of high-grade dysplasia or adenocarcinoma when compared to treatment with a proton pump inhibitor).

There was no statistically significant increase in risk of development of dysplasia or adenocarcinoma between patients who had previously undergone gastric outlet surgery and the rest of the cohort.

Relationship between Symptoms and Cancer Risk

Analysis of symptom duration and type demonstrated that symptoms of heartburn and regurgitation were most prevalent in this cohort. The only symptoms which were predictive of the development of all dysplasia and adenocarcinoma were those grouped in

the swallowing group (dysphagia and odynophagia), which was also true when the analysis was repeated for the development of either high-grade dysplasia and adenocarcinoma or of adenocarcinoma alone. Weight loss was also found to be predictive of the development of these histological groups. The majority of patients had a short duration of symptoms prior to diagnosis of columnar-lined oesophagus (median 2.59 years). The median time from onset of symptoms to diagnosis of columnar-lined oesophagus with intestinal metaplasia was 5.0 years and to low-grade dysplasia was 30.0 years. After 48 years of symptoms, one quarter of the cohort had developed oesophageal adenocarcinoma.
These results add information which is useful in planning screening and surveillance programmes in oesophageal adenocarcinoma prevention.

Validation Studies

The study dealing with the validity of the database has demonstrated that the consistency between observers in the process of retrieving information from the hospital records and entering this data onto the database is most consistent in the data used most frequently in the analyses with poorer consistency in other areas – most notably medications, general epidemiological factors (smoking, alcohol and obesity) and data on symptoms.
The results from this study enable the validity of the previous studies to be evaluated when using them as evidence in the design of screening and surveillance programmes.

Future Studies Following This Project

In addition to continuing the same work as above, with plans made to re-analyse the cohort's risk of adenocarcinoma dependent on segment length and histology with greater patient numbers and follow-up, a number of further projects are planned.

A collaborative study is planned between the US registries at the Mayo Clinic, Rochester, Minnesota, the Cleveland Clinic, Cleveland, Ohio, University of Kansas and Veterans' Affairs Medical Centre, Kansas City, Kansas and University of Southern California, Los Angeles, California and the UK National Barrett's Oesophagus Registry to compare and contrast the United Kingdom and American columnar-lined oesophagus populations.

A case-control study is underway comparing patients with adenocarcinoma to age- and gender-matched controls in the population with columnar-lined oesophagus to examine for risk factors apparent in the adenocarcinoma population with the generation of a scoring system for risk in columnar-lined oesophagus.

A flagging study has been commenced on the same population to examine the outcome in columnar-lined oesophagus and produce robust data on outcome in these patients.

The final study planned is to examine the epidemiology of an entire health region's population with columnar-lined oesophagus.

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Appendix 1

Adenocarcinoma Incidence in Published Series

Author	Country	Year	N Pts	% Male	Mean Age	Treatment	Pt-Yrs FU	N AC	AC Incidence
Cameron[221]	USA	1985	104	67%	59.6	Medical	882	2	0.2%
Cooper[82]	New Zealand	1987	52			Medical	45	0	0.0%
Csendes[133]	Chile	1998	152			Surgery	1147	4	0.4%
Drewitz[36]	USA	1997	170	98%	62	Medical	834	4	0.5%
Ferraris[336]	Italy	1997	187	74%			562	3	0.5%
Hameeteman[337]	Netherlands	1989	50				260	5	1.9%
Iftikar[168]	UK	1992	102	61%	63	Medical	462	4	0.9%
Katz[222]	USA	1998	102	83%	63	11 surgery	563	3	0.5%
McDonald[333]		1996	112				728	3	0.4%
Miros[94]	Australia	1991	81	75%	63	Medical	289	3	1.0%
Moghissi[338]	UK	1993	26				299	4	1.3%
Ovaska[339]	Finland	1989	32				166	3	1.8%
Reid[47]	USA	2000	327	81%	62		1200	43	3.6%
Robertson[340]	UK	1988	56				168	3	1.8%
Spechler[167]	USA	1984	105				350	2	0.6%
Streitz[117]	USA	1998	136				510	7	1.4%
Van der Burgh[84]	Netherlands	1996	155	58%	62		1440	8	0.6%
Murray[216]	UK	2003	2969	57%			11068	29	0.3%
Williamson[93]	USA	1991	176				497	5	1.0%
Wright[341]	UK	1996	166	65%		Medical	461	6	1.3%
Schoenfeld[218]	USA	1998	124	79%	55	Medical	495	0	0.0%
O'Connor[88]	USA	1999	136	67%	58		570	2	0.4%
Eckhardt[230]	Germany	2001	60	58%	61		600	2	0.3%
Attwood[132]	UK	1992	26	46%	70	Medical	78	1	1.3%
Attwood[132]	UK	1992	19	65%	62	Surgery	57	1	1.8%
Brand[264]	USA	1980	10		42	Surgery	50	1	2.0%
Hofsetter[138]	USA	2001	85	78%	57	Surgery	410	0	0.0%
Mabrut[219]	France	2003	26	81%	53	Surgery	128	0	0.0
MacDonald[85]	UK	2000	143	60%	57		629	1	0.2%
Oelschlager[134]	USA	2003	106	63%	50	Surgery	274	1	0.4%
Parilla[260]	Spain	2003	43	77%	50	Medical	215	2	0.9%
Parilla[260]	Spain	2003	58	67%	43	Surgery	348	2	0.6%
Solaymani-Dodoran[169]	UK	2004	1677	62%	64		2600	43	1.7%
Spechler[225]	USA	2001	108	99%	58		1037	4	0.4%
Weston[220]	USA	1999	108	100%	61		362	5	1.4%
Sagar[259]	UK	1995	56	80%	49	Surgery	392	1	0.3%
Nilsson[87]	Sweden	2000	199	70%	59	Medical	797	5	0.6%
Bani-Hani[183]	UK	2000	357				1279	12	0.9%
Pollepalle[342]	USA	1990	220				902	6	0.7%
Total			**8821**				**33155**	**230**	**0.69%**

95% confidence interval for 230 cases (using exact Poisson distribution): 201.23386 to 261.72443

95% confidence interval for annual adenocarcinoma interval modelled using the exact Poisson distribution 0.60-0.79%

Appendix 2

"Form 2" Template

UKBOR Study number_____

Date of form completion_____

Barrett's associated adenocarcinoma natural history study

Data Collection Sheet Dysplasia yes ☐ no ☐ AC yes ☐ no ☐

Name	
Hosp no.	
NHS no.	
DOB	
Address	
GP	

Sex	Male	☐	Female	☐
Civil State	Single	☐	Married	☐
	Not known	☐	Divorced	☐
	Widow(er)ed	☐		
Ethnicity	Arabic	☐	Bangladeshi	☐
	Caucasian	☐	Chinese	☐
	Indian	☐	Pakistani	☐
	Asian other	☐	Black African	☐
	Black Carib	☐	Black other	☐
	Other	☐_____		

Date of death	
1a	
1b	
1c	
2	

UKBOR Study number_____

Main Occupation	
Retired etc.?	

Weight (Kg)

Date	Wt	Date	Wt	Date	Wt
				Height	m

Smoking (tobacco type/day)

Date	Amount	Date	Amount	Date	Amount

Alcohol (type, units per week)

Date	Amount	Date	Amount	Date	Amount

Symptoms

History length			
Retrosternal pain	UGI Bleed	Nausea	
Epigastric pain	Odynophagia	Vomiting	
Acid regurg	Weight loss		
Dysphagia	Belching		
Lifestyle Modification			

UKBOR **Study number_____**

Medical History

Surgical History

Oesoph Dilation		Date	
Fundoplication		Date	
Cholecystectomy		Date	
Gastric Outlet		Date	

UKBOR Study number_____

Medication History

Drug Date								

Family History

Blood Group	

Endoscopy/Other Imaging

Date	OGD/ Ba etc.	Oesoph	Stomach	Duo	Histol	HP test	Result	HP Rx

Comments

Appendix 3

Collaborating Centres

Centre	No. Registered Patients	No. "form 2" completed	No. Patients with some information, but not completed "form 2"	Patients with "form 1" only
Bishop Auckland General Hospital, North Yorkshire (BA)	258	172	84	2
Hemel Hempstead Hospital,Oxfordshire (HH)	89	74	0	15
Landough Hospital, Cardiff South Wales (LP)	140	37	103	0
Ninewells Hospital, Dundee, Scotland (ND)	175	130	1	44
Royal Free Hospital, London (RF)	293	133	0	160
Rotherham General Hospital, South Yorkshire (RY)	506	479	27	0
Wexham Park Hospital, Slough, Oxfordshire (WP)	1290	626	510	154
Total	2751	1651	725	375

Appendix 4

Full Database Content

General Information Table

Field Name	Field Type (length)	Validation Rules
UKBOR No.	Text (6)	No duplicates
Form 2 Done	Yes/No	
Note Retrieval Information	Text (255)	
No Further Information	Yes/No	
Questionable Diagnosis	Yes/No	
Form 2 Entered	Yes/No	
Surname	Text (50)	
Forename	Text (50)	
Gender	Text (1)	"M" or "F"
Date of Birth	Date	>1900 <2000
Date of Diagnosis	Date	>1950 <2006
Hospital No.	Text (20)	
Date of Form 2	Date	>1988
NHS No.	Text (20)	
Marital Status	Text (1)	"S" – single "M" – Married "D" – Divorced "W" – Widow(er)ed "C" – Cohabiting "R" – Residential/Nursing Accomodation
Ethnicity	Text (20)	
Date of Death	Date	>1950 <2006
Cause of Death 1a	Text (255)	
Cause of Death 1b	Text (255)	
Cause of Death 1c	Text (255)	
Cause of Death 2	Text (255)	
Occupation	Text (255)	
Social Class	Text (2)	
Occupation Notes	Text (255)	
Height	Number	>1.00 <2.40
Blood Group	Text (3)	"A-", "A+", "B-", "B+", "AB-", "AB+", "O-" or "O+"
Last Information	Date	>1980 <2006
Date Surveillance Stopped	Date	>1980 <2006
Reason Surveillance Stopped	Text (255)	
Date Symptom Onset	Date	>1920 <2006
Heartburn	Yes/No	
Epigastric Pain	Yes/No	
Abdominal Pain	Yes/No	
Regurgitation	Yes/No	
Nausea	Yes/No	
Dysphagia	Yes/No	
Vomiting	Yes/No	
Belching	Yes/No	
Odynophagia	Yes/No	

Anaemia	Yes/No	
Upper Gastrointestinal Bleed	Yes/No	
Weight Loss	Yes/No	
Night Symptoms	Yes/No	
Presenting Symptoms Notes	Text (255)	
Family History of Columnar-Lined Oesophagus	Text (255)	
Orthopaedic/Rheumatology Comorbidity	Yes/No	
Orthopaedic/Rheumatology Notes	Text (255)	
Neurological Comorbidity	Yes/No	
Neurological Notes	Text (255)	
Gastrointestinal Comorbidity	Yes/No	
Oesophageal Dysmotility	Yes/No	
Mediastinal Radiotherapy	Yes/No	
Mediastinal Radiotherapy Date	Date	>1920 <2006
Inflammatory Bowel Disease	Yes/No	
Appendicectomy	Yes/No	
Bowel Surgery	Yes/No	
Stomach Cancer	Yes/No	
Colorectal Cancer	Yes/No	
Liver Disease	Yes/No	
Gastrointestinal Comorbidity Notes	Text (255)	
Genitourinary Comorbidity	Yes/No	
Benign Prostatic Hypertrophy	Yes/No	
Prostate Cancer	Yes/No	
Prostatectomy	Yes/No	
Fibroids	Yes/No	
Hysterectomy	Yes/No	
Genitourinary Notes	Text (255)	
Haematology Comorbidity	Yes/No	
Haematology Notes	Text (255)	
Superficial Lesion Comorbidity	Yes/No	
Breast Cancer	Yes/No	
Thyroid Disease	Yes/No	
Skin Malignancy	Yes/No	
Superficial Lesion Notes	Text (255)	
Respiratory Comorbidity	Yes/No	
Chronic Obstructive Pulmonary Disease	Yes/No	
Pneumoconiosis	Yes/No	

Bronchial Cancer	Yes/No	
Respiratory Comorbidity Notes	Text (255)	
Cardiovascular Comorbidity	Yes/No	
Ischaemic Heart Disease	Yes/No	
Cardiac Failure	Yes/No	
Peripheral Vascular Disease	Yes/No	
Cerebrovascular Disease	Yes/No	
Arrhythmia	Yes/No	
Hypertension	Yes/No	
Diabetes	Yes/No	
Cardiovascular Notes	Text (255)	
Oesophageal Dilatation	Yes/No	
Cholecystectomy	Yes/No	
Cholecystectomy Date	Date	>1920 <2006
Fundoplication	Yes/No	
Fundoplication Date	Date	>1920 <2006
Fundoplication Type	Text (50)	
Post-Fundoplication Symptoms	Text (255)	
Fundoplication Notes	Text (255)	
Gastric Outlet Surgery	Yes/No	
Gastric Outlet Surgery Date	Date	>1920 <2006
Adenocarcinoma Treatment	Yes/No	
Adenocarcinoma Treatment Type	Text (255)	
Adenocarcinoma Treatment Date	Date	>1920 <2006
Adenocarcinoma Treatment Outcome	Text (255)	
Adenocarcinoma Notes	Text (255)	
Smoking Notes	Text (255)	
Alcohol Notes	Text (255)	
Patient Address Line 1	Text (255)	
Patient Address Line 2	Text (255)	
Patient Address Line 3	Text (255)	
Patient Address Line 4	Text (255)	
Patient Postcode	Text (10)	
Patient Telephone No.	Text (16)	
GP Name	Text (255)	
GP Address Line 1	Text (255)	
GP Address Line 2	Text (255)	
GP Address Line 3	Text (255)	
GP Address Line 4	Text (255)	
GP Postcode	Text (10)	
GP Telephone No.	Text (16)	
Death Certificate	Yes/No	

Requested		
Death Certificate Obtained	Yes/No	

Alcohol Table

Field Name	Field Type	Validation Rule
UKBOR No.	Text (6)	
Date	Date	>1920 <2006
Score	Integer	>0 <5

Medication Table

Field Name	Field Type	Validation Rule
UKBOR No.	Text (6)	
Date	Date	>1920 <2006
PPI use	Yes/No	
H2RA Use	Yes/No	
Aspirin Use	Yes/No	
NSAID Use	Yes/No	
Steroid Use	Yes/No	
Beta Agonist Use	Yes/No	
Calcium Channel Blocker Use	Yes/No	
H Pylori Eradication	Yes/No	
Other Medications	Text (255)	

Endoscopy Table

Field Name	Field Type	Validation Rule
UKBOR No.	Text (6)	
Date	Date	>1950 <2006
Indication	Text (1)	"D" – Diagnostic "S" – Surveillance "N" – New Symptoms During Surveillance "F" – Follow-Up of Other Condition "P" – Post-Oesophagectomy
Squamocolumnar Junction Level	Integer	>15 <50
Non-circumferential Proximal Extent of Columnar Mucosa Level	Integer	>15 <50
Oesophagogastric Junction Level	Integer	>25 <50
Visual Diagnosis of Columnar-Lined Oesophagus	Yes/No	
Stated Length of Circumferential Columnar-Lined Oesophagus	Integer	-3 – "Short" Segment 99 – "Long" Segment
Diaphragmatic Hiatus Level	Integer	>25 <50
Oesophagitis	Yes/No	
Oesophageal Ulcer	Yes/No	
Oesophagitis Grade/Notes	Text (50)	
Proximal Oesophagitis Level	Integer	>15 <50
Hiatus Hernia	Yes/No	
Oesophageal Stricture	Yes/No	
Oesophageal Stricture Level	Integer	>15 <50
Oesophageal Dilatation	Yes/No	
Adenocarcinoma	Yes/No	
Adenocarcinoma Level	Integer	>15 <50
Gastritis	Yes/No	
Gastric Ulcer	Yes/No	
Duodenitis	Yes/No	
Duodenal Ulcer	Yes/No	
Endoscopy Notes	Text (255)	

Histology Table

Field Name	Field Type	Validation Rule
UKBOR No.	Text (6)	
Date	Date	>1950 <2006
Histology Site (Level)	Integer	>15 <50
Histology Site	Text (50)	
Number of Biopsy Samples	Integer	<200
Four-Quadrant Biopsy Technique	Yes/No	
Squamous Mucosa	Yes/No	
Oesophageal Glands	Yes/No	
Columnar Mucosa	Yes/No	
Intestinal Metaplasia	Yes/No	
Complete Intestinal Metaplasia	Yes/No	
Gastric Mucosa (Unspecified Type)	Yes/No	
Gastric Body Mucosa	Yes/No	
Gastric Cardia Mucosa	Yes/No	
Gastric Fundic Mucosa	Yes/No	
Disorderly Cardiac Glandular Mucosa	Yes/No	
Acute Inflammation	Yes/No	
Chronic Inflammation	Yes/No	
Indefinite Changes for Dysplasia in Presence of Inflammation	Yes/No	
Indefinite Changes for Dysplasia Not in Presence of Inflammation	Yes/No	
Low-Grade Dysplasia	Yes/No	
High-Grade Dysplasia	Yes/No	
Adenocarcinoma	Yes/No	
Helicobacter Pylori	Yes/No	
Histology Notes	Text (255)	

H. Pylori Table

Field Name	Field Type	Validation Rule
UKBOR No.	Text (6)	
Date	Date	>1950 <2006
Test Type	Text (50)	
Test Positive	Yes/No	

Smoking Table

Field Name	Field Type	Validation Rule
UKBOR No.	Text (6)	
Date	Date	>1920 <2006
Score	Integer	>0 <6

Weight Table

Field Name	Field Type	Validation Rule
UKBOR No.	Text (6)	
Date	Date	>1920 <2006
Weight	Integer	>20 <300

Appendix 5

Smoking and Alcohol Groups

Smoking Groups

Cigarette Smoking Habit	Smoking Group
≥20 cigarettes/day	5
<20 cigarettes/day	4
Ceased smoking within 10 years	3
Ceased smoking >10 years	2
Never smoked	1

Alcohol Consumption Groups

Weekly Alcohol Consumption (units)		Alcohol Group
Males	Females	
≤9	≤7	1
>9 ≤21	>7 ≤14	2
>21 ≤40	>14 ≤30	3
>40	>30	4

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